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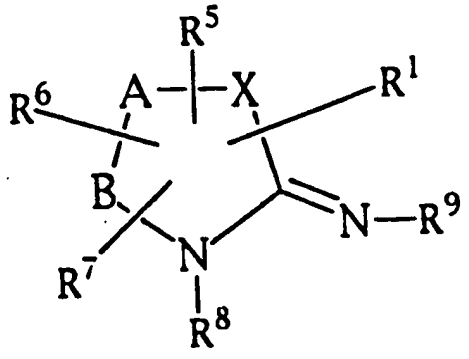
(54) Title: NITRIC OXIDE SYNTHASE INHIBITORS DERIVED FROM CYCLIC AMIDINES

(57) Abstract

Compounds having formula (I) wherein R^1, R^5, R^6 and R^7 are hydrogen or certain specified substituents; R^8 and R^9 are independently hydrogen, hydroxy or alkoxy; and X, A and B are independently NR^2, O, S, SO, SO_2, CH–CH or $(CH_2)p$, p being 0-6; are useful as nitric oxide synthase inhibitors.



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Nitric Oxide Synthase Inhibitors Derived from Cyclic Amidines

This application is a continuation-in-part of U.S. Serial No. 08/438,321, filed May 10, 1995, the contents of which are herein incorporated by reference.

Field of the Invention

The present invention relates to amidino derivative compounds, pharmaceutical compositions containing these novel compounds, and to their use in therapy, in particular their use as nitric oxide synthase inhibitors.

Background of the Invention

It has been known since the early 1980's that the vascular relaxation brought about by acetylcholine is dependent on the presence of the endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity of nitric oxide (NO) as a vasodilator has been known for well over 100 years and NO is the active component of amyl nitrite, glyceryl trinitrate and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway by which NO is synthesized from the amino acid L-arginine by the enzyme NO synthase.

NO is the endogenous stimulator of the soluble guanylate cyclase and is involved in a number of biological actions in addition to endothelium-dependent relaxation including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al, Biochemical Pharmacology, 38, 1709-1715 (1989) and Moncada et al, Pharmacological Reviews, 43, 109-142 (1991).

It is now thought that excess NO production may be involved in a number of conditions, particularly conditions which involve

systemic hypotension such as toxic shock and therapy with certain cytokines.

The synthesis of NO from L-arginine can be inhibited by the L-arginine analogue, L-N-monomethyl-arginine (L-NMMA) and the therapeutic use of L-NMMA for the treatment of toxic shock and other types of systemic hypotension has been proposed (WO 91/04024 and GB-A-2240041). The therapeutic use of certain other NO synthase inhibitors apart from L-NMMA for the same purpose has also been proposed in WO 91/04024 and in EP-A-0446699.

It has recently become apparent that there are at least three types of NO synthase as follows:

(i) a constitutive, Ca^{++}/calmodulin dependent enzyme, located in the endothelium, that releases NO in response to receptor or physical stimulation.

(ii) a constitutive, Ca^{++}/calmodulin dependent enzyme, located in the brain, that releases NO in response to receptor or physical stimulation.

(iii) a Ca^{++} independent enzyme which is induced after activation of vascular smooth muscle, macrophages, endothelial cells, and a number of other cells by endotoxin and cytokines. Once expressed this inducible NO synthase synthesizes NO for long periods.

The NO released by the constitutive enzymes acts as a transduction mechanism underlying several physiological responses. The NO produced by the inducible enzyme is a cytotoxic molecule for tumor cells and invading microorganisms. It also appears that the adverse effects of excess NO production, in particular pathological vasodilation and tissue damage, may result largely from the effects of NO synthesized by the inducible NO synthase.

There is also a growing body of evidence that NO may be involved in the degeneration of cartilage which takes place in certain conditions such as arthritis and it is also known that NO synthesis is increased in rheumatoid arthritis. Accordingly,

further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune and/or inflammatory conditions affecting the joints, for example arthritis, inflammatory bowel disease, cardiovascular ischemia, diabetes, hyperalgesia (allodynia), cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia, secondary to cardiac arrest), and other CNS disorders mediated by NO, including opiate tolerance in patients needing protracted opiate analgesics, benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behaviors for example nicotine and eating disorder.

Further conditions in which there is an advantage in inhibiting NO production from L-arginine include systemic hypotension associated with septic and/or toxic shock induced by a wide variety of agents; therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy. Further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune diseases and/or inflammatory conditions such as those affecting the joints, for example arthritis or ARDS or inflammatory bowel disease, or asthma, cardiovascular ischemia, congestive heart failure, myocarditis, artherosclerosis, migraine, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, and diabetes.

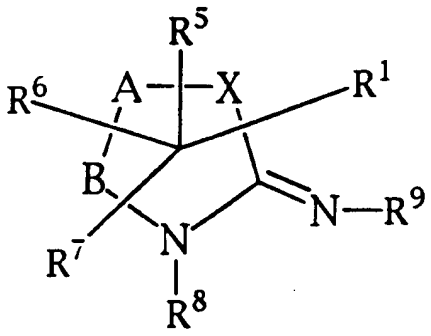
Some of the NO synthase inhibitors proposed for therapeutic use so far, and in particular L-NMMA, are non-selective in that they inhibit both the constitutive and the inducible NO synthase. Use of such a non-selective NO synthase inhibitor requires that great care be taken in order to avoid the potentially serious consequences of over-inhibition of the constitutive NO-synthase including hypertension and possible thrombosis and tissue damage. In particular, in the case of the therapeutic use of L-NMMA for the treatment of toxic shock it has been recommended that the patient must be subject to continuous blood pressure monitoring throughout the treatment. Thus, while non-selective NO synthase inhibitors have

therapeutic utility provided that appropriate precautions are taken, NO synthase inhibitors which are selective in the sense that they inhibit the inducible NO synthase to a considerably greater extent than the constitutive isoforms of NO synthase would be of even greater therapeutic benefit and easier to use.

WO94/12165, WO94/14780, WO93/13055, EP0446699A1 and U.S. Patent No. 5,132,453 disclose compounds that inhibit nitric oxide synthesis and preferentially inhibit the inducible isoform of nitric oxide synthase. The disclosures of which are hereby incorporated by reference in their entirety as if written herein.

Summary of the Invention

In accordance with the present invention novel amidino derivatives are provided. These novel inhibitor compounds can be represented by the following chemical formula (I):



(I)

and salts, and pharmaceutically acceptable esters and prodrugs thereof, wherein:

R^1 is selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, alkyloxy, thioalkoxy, cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocyclyl, aryl, hydroxy, lower alkoxy, aryloxy, thiol, lower thioalkoxy, halogen, cyano, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl, alkylaminoaryl, acylamino, carboxy,

carboxyalkyl, $CONR^{10}R^{11}$, $S(O)R^{10}$, $S(O)_2R^{10}$, $SO_2NR^{10}R^{11}$, $PO(OR^{10})(OR^{11})$, amidino, guanidino;

wherein all said substitutions may be optionally substituted with one or more of the following: halogen, lower alkyl, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, $S(O)R^{10}$, $S(O)_2R^{10}$, amidino, guanidino;

X = NR^2, O, S, SO, SO_2, $(CH_2)_p$, CH=CH;

p = 0 to 6;

A = NR^3, O, S, SO, SO_2, $(CH_2)_q$, CH=CH;

q = 0 to 6;

B = NR^4, O, S, SO, SO_2, $(CH_2)_v$, CH=CH;

v = 0 to 6;

R^2 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^3 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^4 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^5, R^6, R^7 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, halogen, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl, alkylaminoaryl, acylamino, carboxyl, carboalkoxy, carboaryloxy, carboarylalkyloxy, cyano, aminocarbonylalkoxy, aminocarbonylamino, aminocarbonylaminoalkyl, haloalkyl, $SO_2NR^{10}R^{11}$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy;

R^5, R^6, may optionally be taken together to form an alicyclic hydrocarbon, heterocyclyl or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:

lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

R^8 = hydrogen, hydroxy, O-Alkyl;
R^9 = hydrogen, hydroxy, O-Alkyl;
R^{10} = hydrogen, lower alkyl, alkylaryl, aryl;
R^{11} = hydrogen, lower alkyl, alkylaryl, aryl;
R^{10} and R^{11}, taken together, may be alkylene, resulting in a N-containing heterocycle;

With the proviso that when R^1 is lower alkyl, lower alkenyl, or lower alkynyl, R^1 cannot be optionally substituted by cycloalkyl, heterocyclyl, and aryl, unless one A, or B is NR^2, O, S, SO, SO_2;

With the proviso that when A and B are $(CH_2)_p$ or CH=CH, and R^1 is lower alkyl, lower alkenyl, or lower alkynyl, R^1 is not substituted by cycloalkyl, heterocyclyl, or aryl and R^5 and R^6 are not H;

With the proviso that only one of X, A, and B, may be selected from NR^2, NR^3, NR^4 respectively, or O, S, SO, or SO_2;

With the further proviso that when $X=(CH_2)p$; $A=(CH_2)q$, $B=(CH_2)v$, p+q+v=3, then no more than one of R^1, R^5, R^6 and R^7 can be alkyl, alkoxy, cycloalkyl or cycloalkoxy at the 5-position;

With one further proviso that when $X=(CH_2)p$; $A=(CH_2)q$, $B=(CH_2)v$, p+q+v=3, and one of R^1, R^5, R^6 and R^7 is an alkyl, cycloalkyl or aryl group at the 5-position, then none of the remaining R^1, R^5, R^6 and R^7 can be a cyano, substituted amino, alkoxy or thioalkoxy at the 5-position;

With the further proviso that when X=CH=CH, $A=(CH_2)q$, $B=(CH_2)v$ and q+v=2, then none of R^1, R^5, R^6 and R^7 can be carboxy at the 6-position; and

With the further proviso that when X=NH, $A=(CH_2)q$, $B=(CH_2)v$ and q+v=4, then none of R^1, R^5, R^6 and R^7 can be carboxy at the 7-position.

In another broad aspect, the present invention is directed to inhibiting nitric oxide synthesis in a subject in need of such inhibition or treatment by administering a compound of Formula (I) which preferentially inhibits the inducible isoform of nitric oxide synthase over the constitutive isoform of nitric oxide synthase, in a nitric oxide synthesis inhibiting amount to such subject.

The invention further relates to a pharmaceutical composition comprising a compound from Formula (I).

Compounds and compositions defined above have usefulness as inhibitors of nitric oxide synthase. These compounds also preferentially inhibit the inducible form.

Conditions in which there is an advantage in inhibiting NO production from L-arginine in disorders mediated by nitric oxide including amongst others, systemic hypotension associated with septic and/or toxic shock induced by a wide variety of agents; therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy. Further conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune diseases and/or inflammatory conditions such as those affecting the joints, for example arthritis or inflammatory bowel disease, cardiovascular ischemia, diabetes, congestive heart failure, myocarditis, artherosclerosis, migraine, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, hyperalgesia (allodynia) cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia, secondary to cardiac arrest) and other CNS disorder mediated by NO, including opiate tolerance in patients needing protracted opiate analgesics, benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behaviors for example nicotine and eating disorder.

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic

acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulfuric, citric, tartaric, phosphoric, lactic, acetic, succinic, fumaric, maleic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, benzenesulfonic and the like. (See, for example, S. M. Berge et al., Pharmaceutical Salts, *J. Pharm. Sci.*, **1977**, *66*, 1-19.) Salts of the compounds of formula (I) can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

While it may be possible for the compounds of formula (I) to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. According to a further aspect, the present invention provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, inhalation, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with

liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Formulations for inhalation administration where the active ingredient is inhaled into the lungs either as a mist or co-administered with an inert carrier agent.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention may be administered orally or via injection at a dose of from 0.001 to 2500 mg/kg per day. The dose range for adult humans is generally from 0.005 mg to 10 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The compounds of formula (I) are preferably administered orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age

and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

As utilized herein, the term "lower alkyl", alone or in combination, means an acyclic alkyl radical containing from 1 to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like.

The term "lower alkenyl" refers to an unsaturated acyclic hydrocarbon radical in so much as it contains at least one double bond. Such radicals containing from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Examples of suitable alkenyl radicals include propylenyl, buten-1-yl, isobutenyl, pentenylen-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "lower alkynyl" refers to an unsaturated acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Examples of suitable alkynyl radicals include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "alicyclic hydrocarbon" or "cycloalkyl" means a aliphatic radical in a ring with 3 to about 10 carbon atoms, and preferably from 3 to about 6 carbon atoms. Examples of suitable alicyclic radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl and the like.

The term "aromatic hydrocarbon" means aromatic radical with 4 to about 16 carbon atoms, preferably 6 to about 12 carbon

atoms, more preferably 6 to about 10 carbon atoms. Examples of suitable aromatic hydrocarbon radicals include phenyl, naphthyl, and the like.

The term "aryl" as used herein means 5- and 6-membered single-aromatic radicals which may include from zero to four heteroatoms. Representative aryls include phenyl, thienyl, furanyl, pyridinyl, (is)oxazoyl and the like.

The term DCM means dichloromethane.

The term DEAD means diethyl azodicarboxylate.

The term DIBAL-H means diisobutylaluminum hydride.

The term DMAP means dimethylaminopyridine.

The term DMSO means dimethylsulfoxide.

The term EDC means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

The term "heterocyclyl radical" means a saturated or unsaturated cyclic hydrocarbon radical including aromatic systems with 4 to about 10 carbon atoms, preferably about 5 to about 6; wherein 1 to about 4 carbon atoms are replaced by nitrogen, oxygen, sulfur, or carbonyl. The "heterocyclic radical" may be fused to an aromatic hydrocarbon radical. Suitable examples include pyrrolyl, pyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, indolyl, thienyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolinyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like.

The term HOBT means N-hydroxybenzotriazole.

The term "lower alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above and most preferably containing 1 to about 4 carbon atoms. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "lower thioalkoxy", alone or in combination, means an alkyl thioether radical wherein the term alkyl is as defined above and most preferably containing 1 to about 4 carbon atoms. Examples of suitable alkyl thioether radicals include thiomethoxy, thioethoxy, thio-n-propoxy, thio-i-propoxy, thio-n-butoxy, thio-iso-butoxy, thio-sec-butoxy, thio-tert-butoxy and the like.

The term alkoxycarbonyl as used herein means an alkoxy group, as defined above, having a carbonyl (C=O) group attached.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term MCPBA means m-chloroperbenzoic acid.

The term NMM means N-methylmorpholine.

The term NMMO means 4-methylmorpholine N-oxide.

The term "prodrug" refers to a compound that is made more active *in vivo*.

The term sulfinyl means SO.

The term sulfonyl means SO_2.

The term TEA means triethylamine.

The term $TMSN_3$ means azidotrimethylsilane.

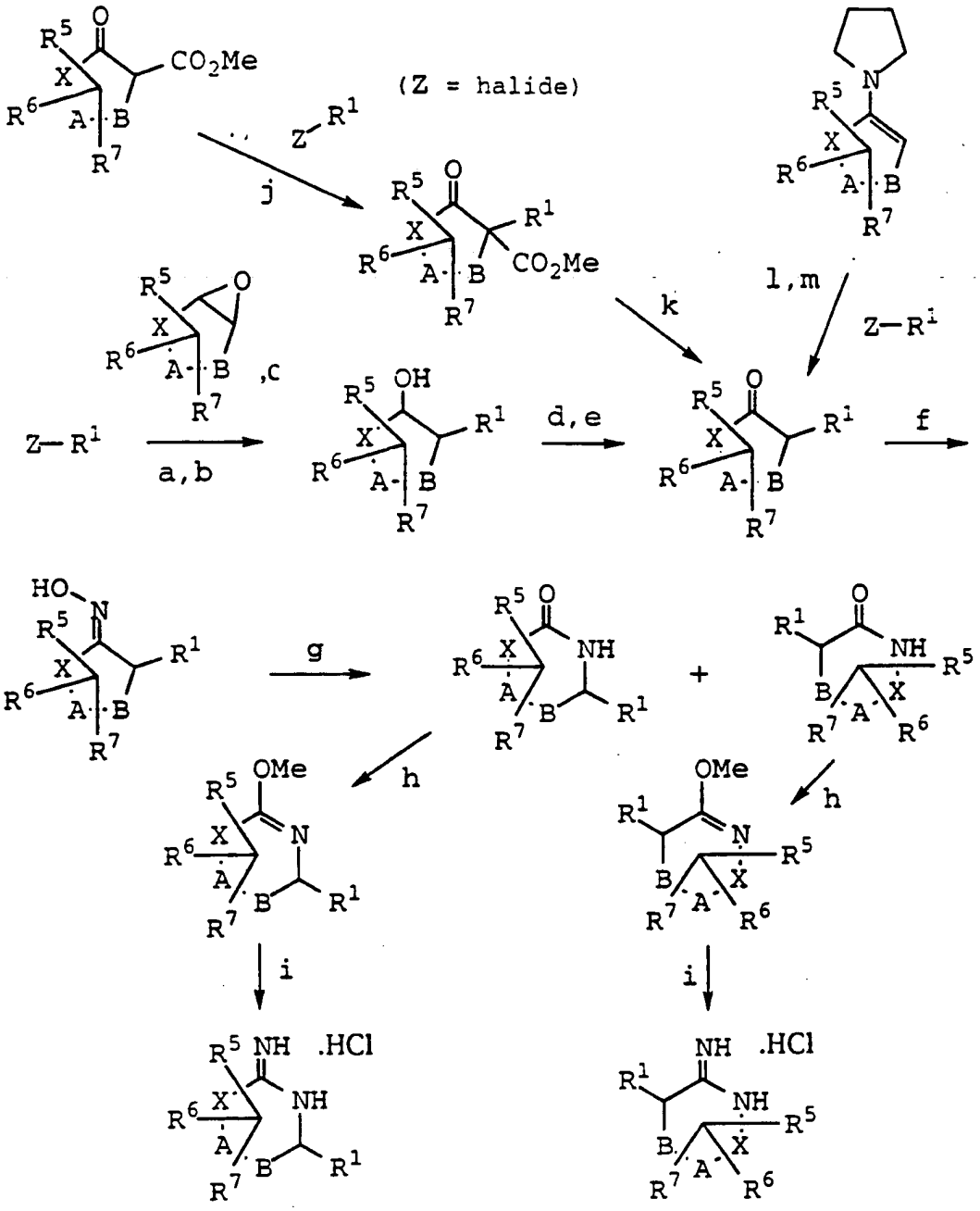
As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

Compounds of the present invention can exist in geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention.

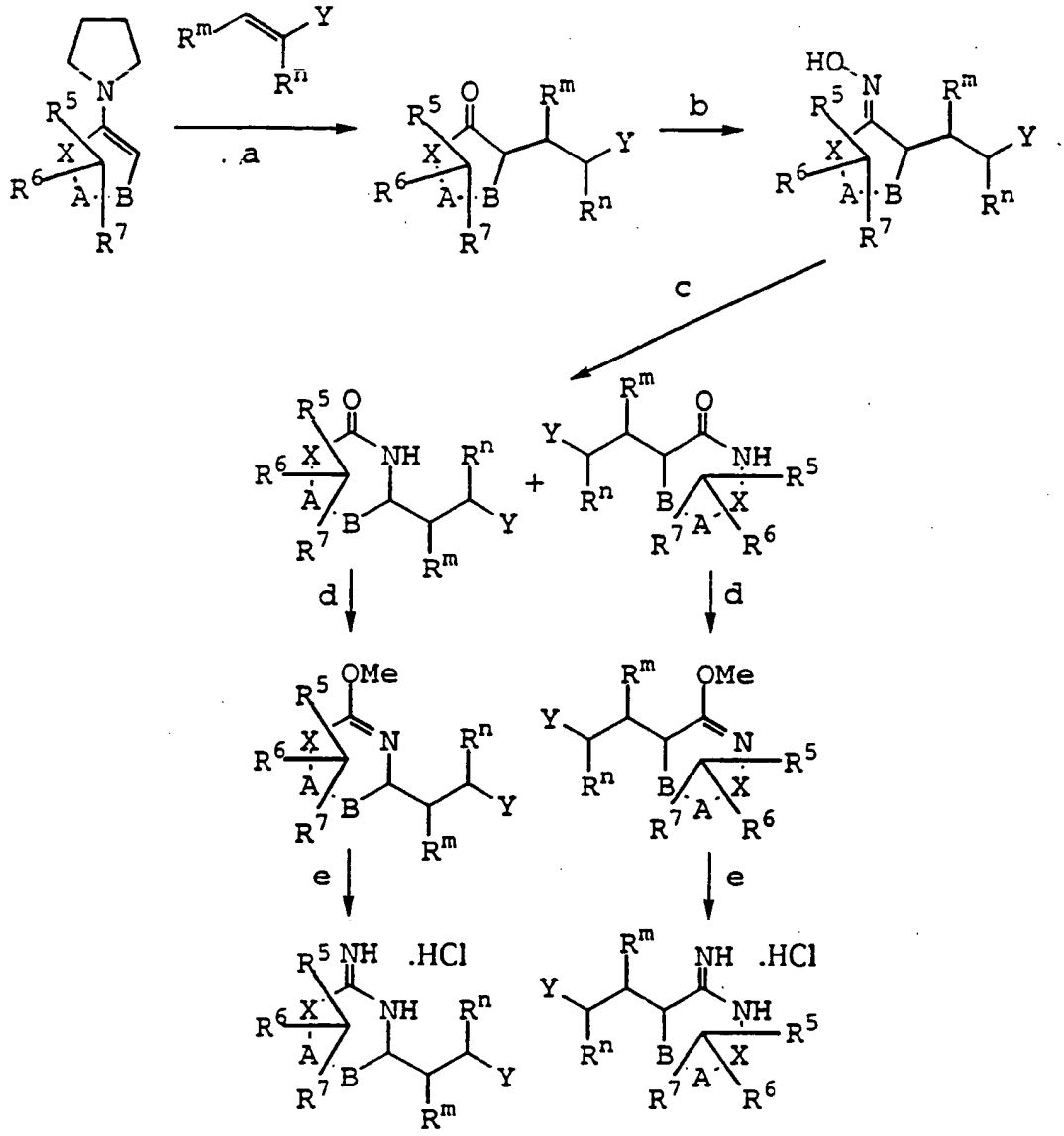
Disclosed are eleven general synthetic processes useful in the preparation of the compounds of the present invention.

Scheme 1:



a) Mg, THF; b) CuI, -30 °C; c) -30 °C to 0 °C or r.t.; d) DMSO, oxalyl chloride, CH_2Cl_2, -70 °C; e) Et_3N, -70 °C to 0 °C; f) NH_2OH, NaOAc, EtOH; g) $PhSO_2Cl$, NaOH, H_2O, acetone; h) $Me_3O^+BF_4^-$; i) NH_4Cl; j) K_2CO_3 or NaH, DMF; k) NaCN, DMSO, H_2O, heat l) DMF, L- R^1 (where L'-R^1 is CH_2=CHCO-R^1); m) 1N LiOH, MeOH.

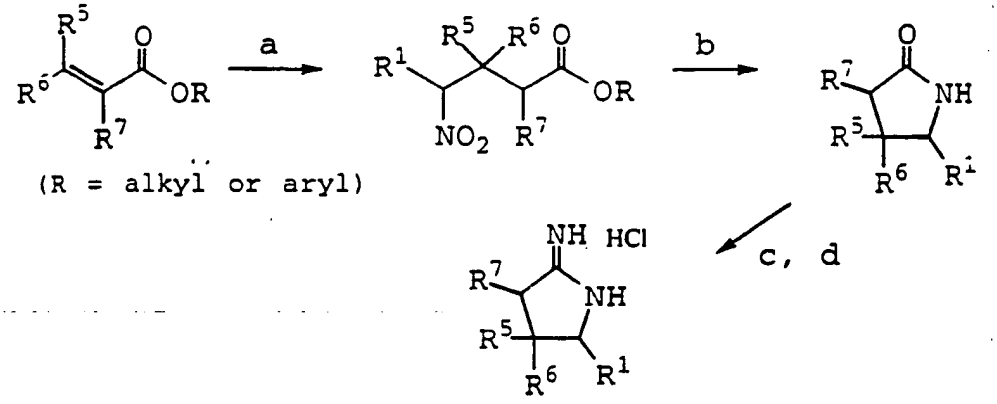
Scheme 2:



(Y = CN, COOalkyl, NO_2, SO_2alkyl,
SO_2NH_2, $SO_2NR^{10}R^{11}$, heteroaryl)
R^m = H, alkyl, cycloalkyl, aryl, heterocycle
R^n = H, alkyl, aryl, heterocycle
R^m and R^n may be taken together to form a ring

a) solvent (benzene); b) NH_2OH, NaOAc, EtOH; c) $PhSO_2Cl$, NaOH, H_2O, acetone; d) $Me_3O^+BF_4^-$, CH_2Cl_2; e) NH_4Cl, MeOH.

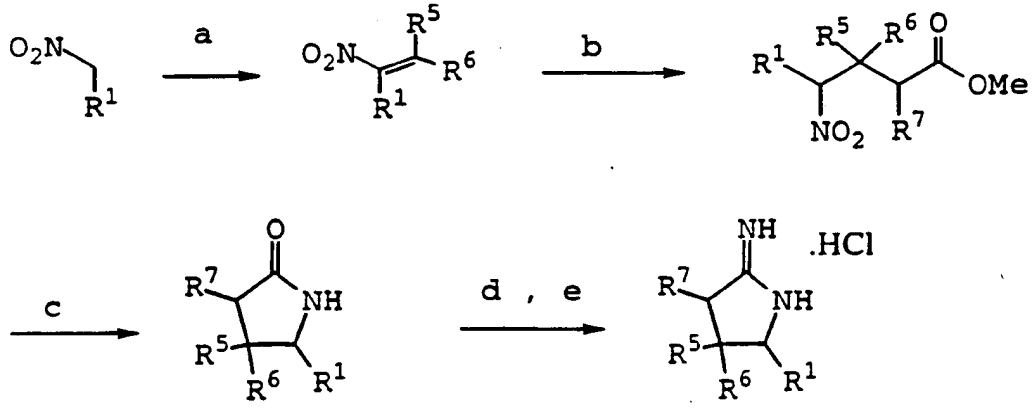
Scheme 3:



(R = alkyl or aryl)

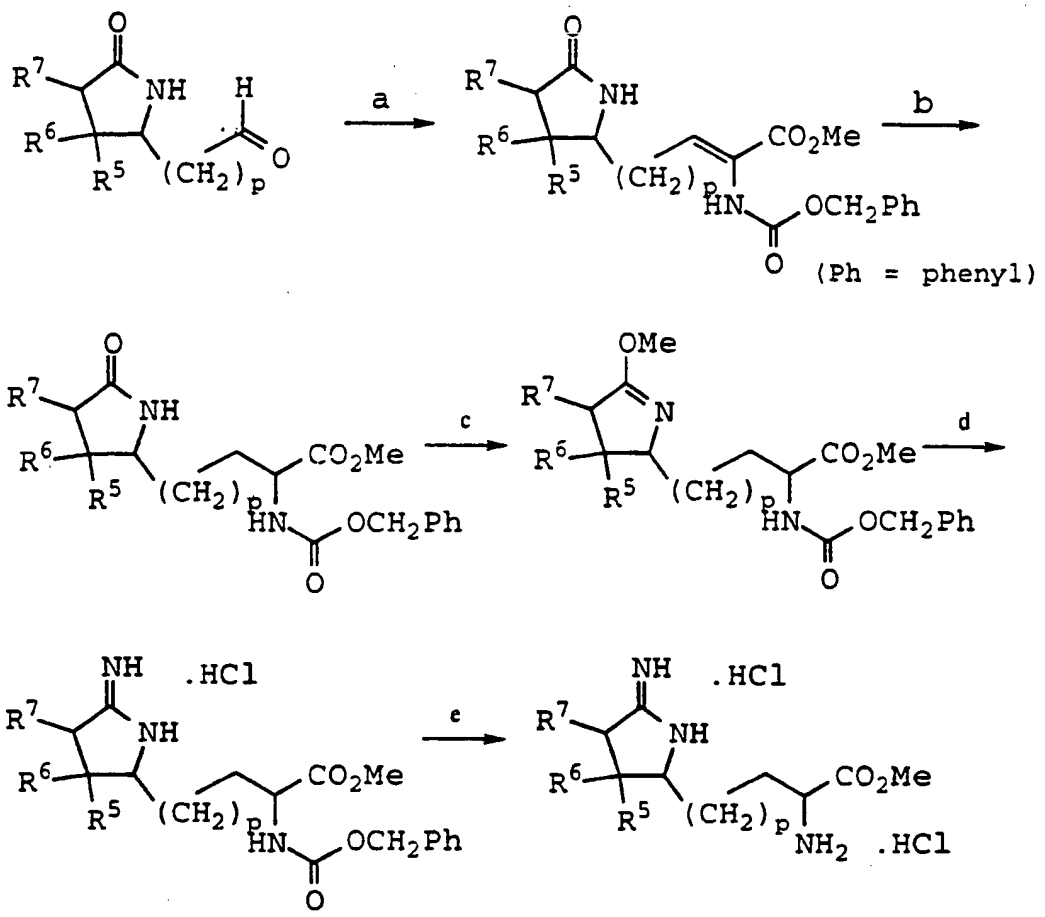
a) Base, $R^1CH_2NO_2$ b) H_2 / RaNi, 55°C c) $Me_3O^+BF_4^-$, CH_2Cl_2; d) NH_4Cl, MeOH

Scheme 4:



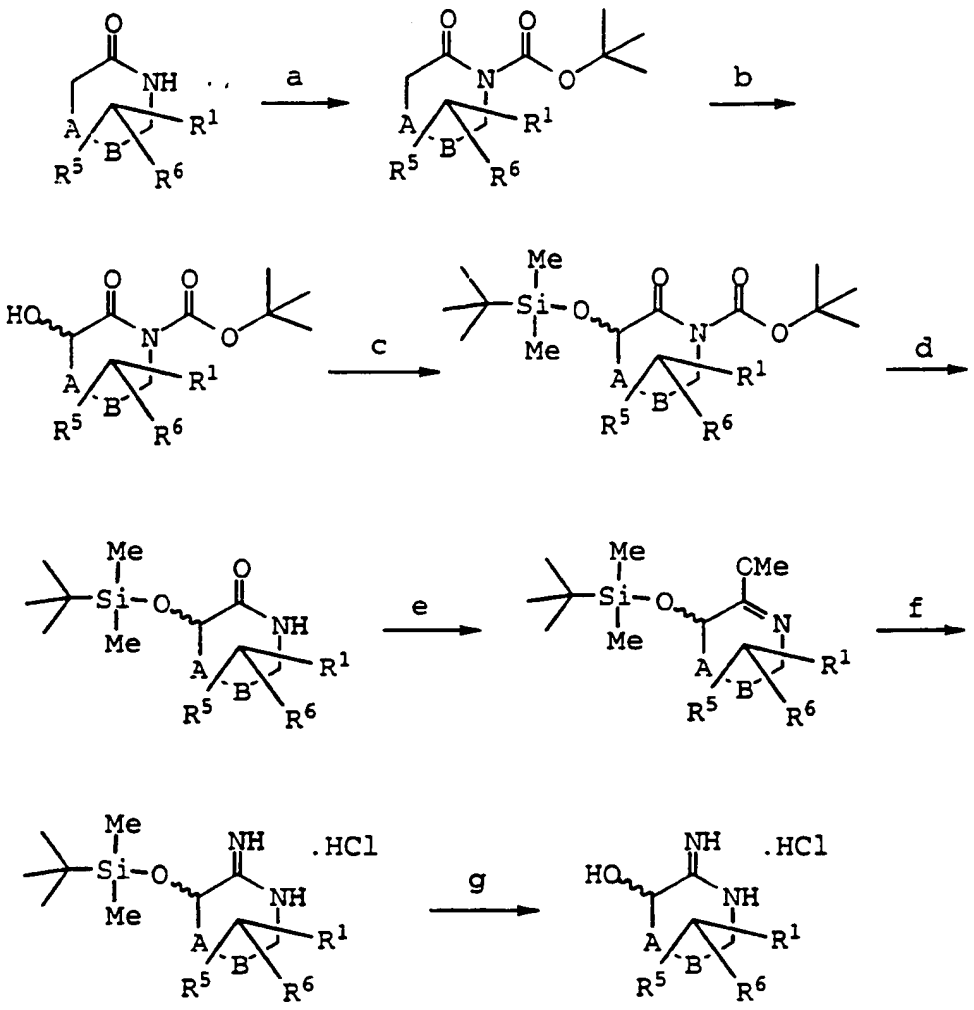
a) R^5COR^6 base; b) Base, $R^7CH_2CO_2Me$; c) H_2/RaNi, 55°C; d) $Me_3O^+BF_4^-$, CH_2Cl_2; e) NH_4Cl, MeOH.

Scheme 5:



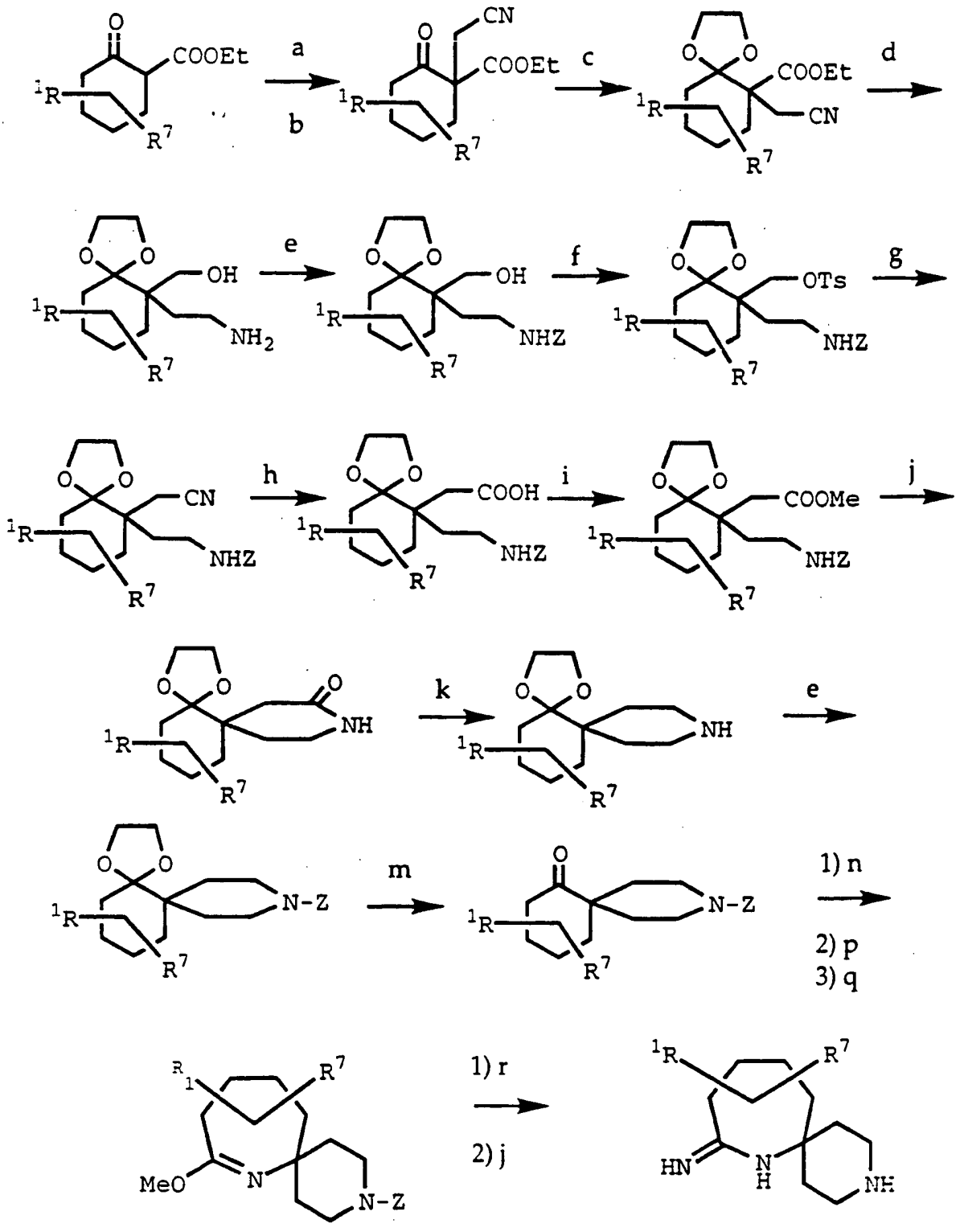
a) DBU, Z-α-phosphonoglycine trimethyl ester; b) H_2/ [Rh[(COD)(R,R-DIPAMP)]$^+BF_4^-$ (antipod catalyst can be used);
c) Me_3O^+ BF_4^-, CH_2Cl_2; d) NH_4Cl,MeOH; e) H_2, Pd/C.

Scheme 6:



a) (t-butylOCO)$_2$O, DMAP, THF; b) LiHMDS, HMPA, THF, (1S)-(+)-(10-camphorsulfonyl)oxaziridine or (1R)-(-)-(10-camphorsulfonyl) oxaziridine; c) t-butyldimethylsilyl chloride, imidazole, DMF; d) $Mg(ClO_4)_2$ (20%), CH_3CN; e) $Me_3O^+BF_4^-$, CH_2Cl_2; f) NH_4Cl, MeOH; g) $(butyl)_4N^+F^-$, MeOH.

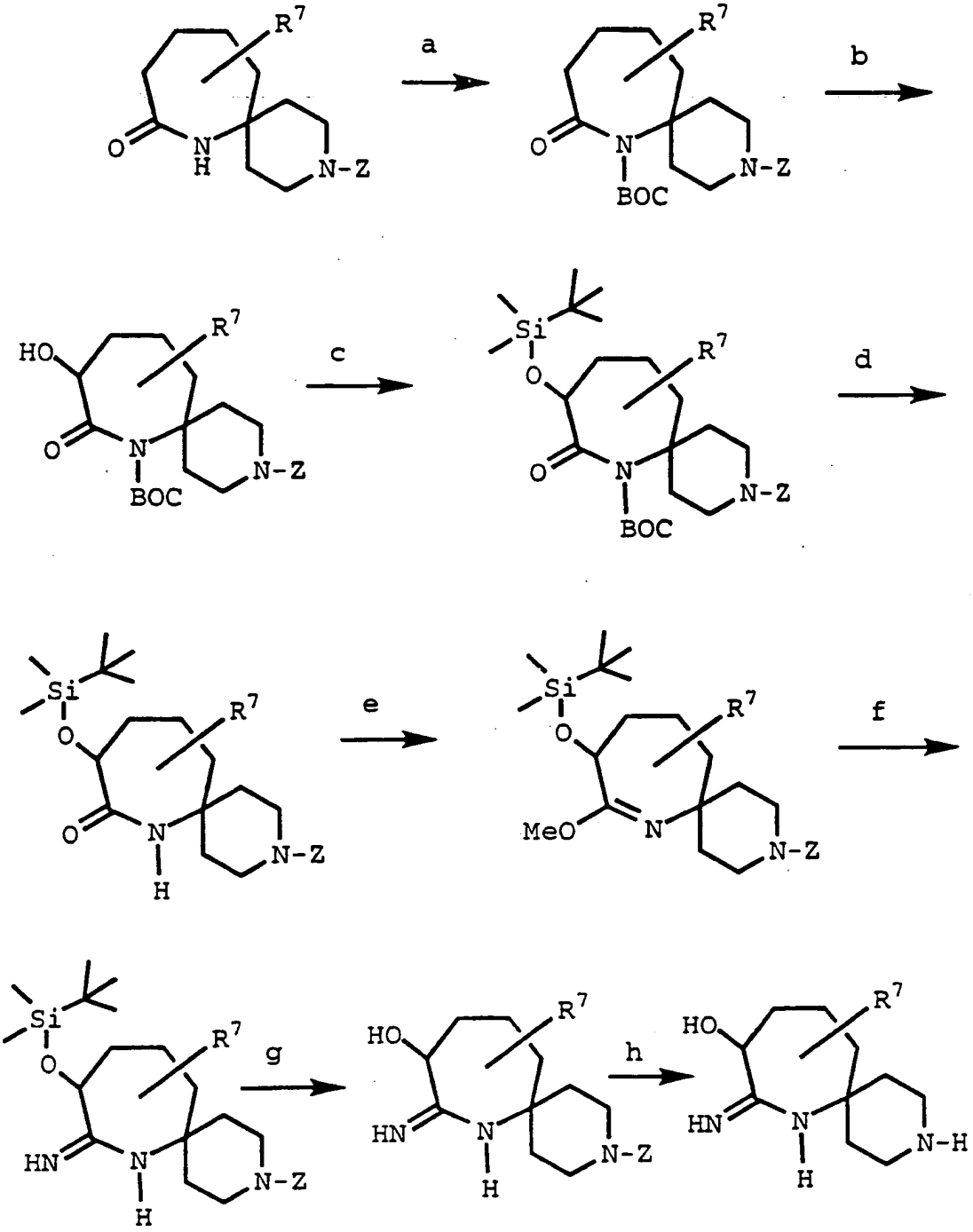
Scheme 7:



a) NaH/THF; b) $BrCH_2CN$/THF; c) Ethylene glycol/p-toluenesulfonic acid/toluene; d) $LiAlH_4/Et_2O$; e) Carbobenzoxy chloride/t-butanol/water/NaOH; f) p-Toluenesulfonyl chloride/CH_2Cl_2/pyridine; g)

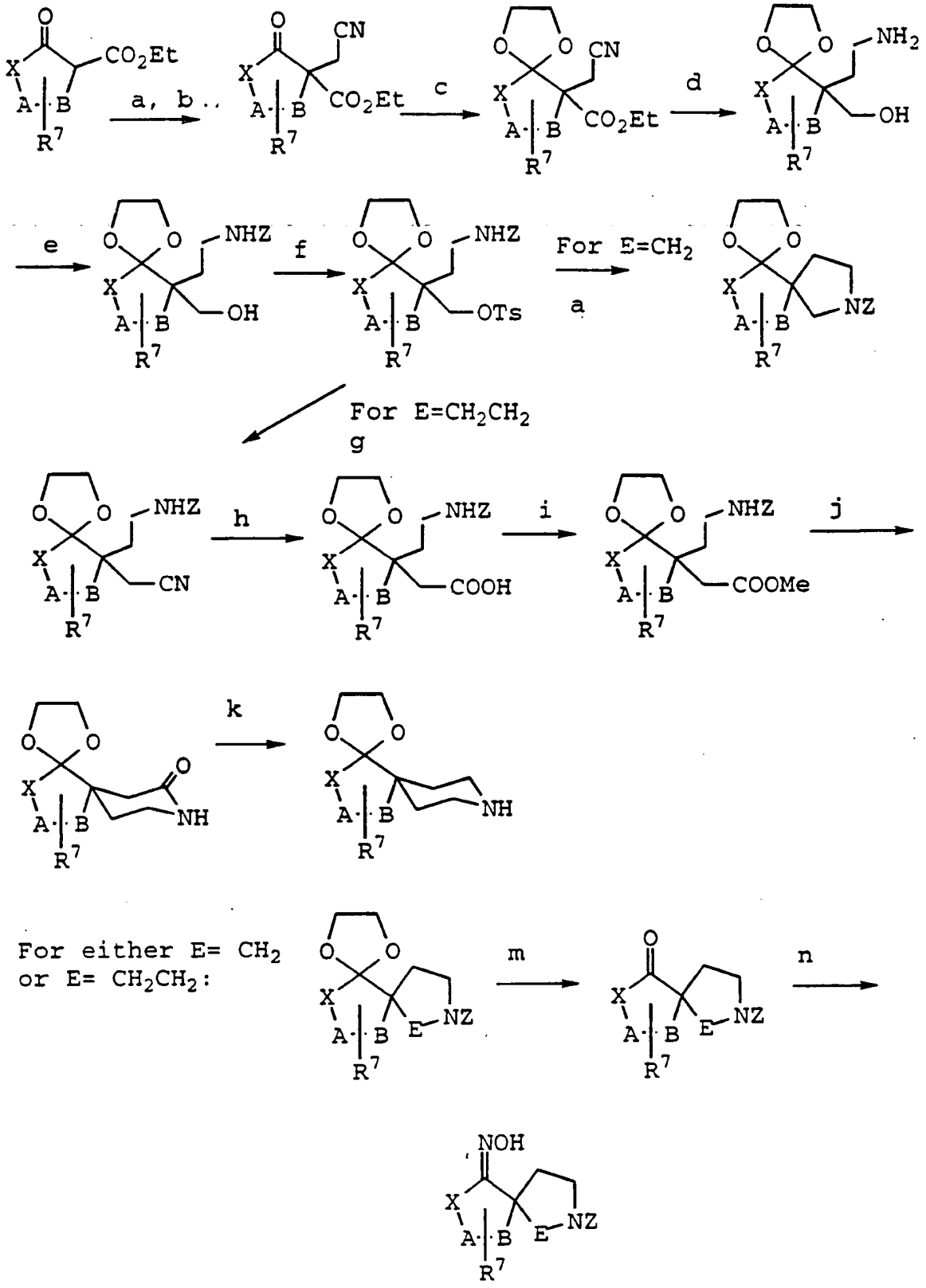
KCN/acetonitrile; h) KOH/ethylene glycol; i) MeI/DMF/$NaHCO_3$; j) H_2/Pd/MeOH; k) B_2H_6/THF; m) HCl/AcOH/H_2O; n) NH_2OH; p) Benzenesulfonyl chloride/ H_2O/acetone NaOH; q) Trimethyloxonium tetrafluoroborate; r) NH_4Cl/MeOH;

Scheme 8:

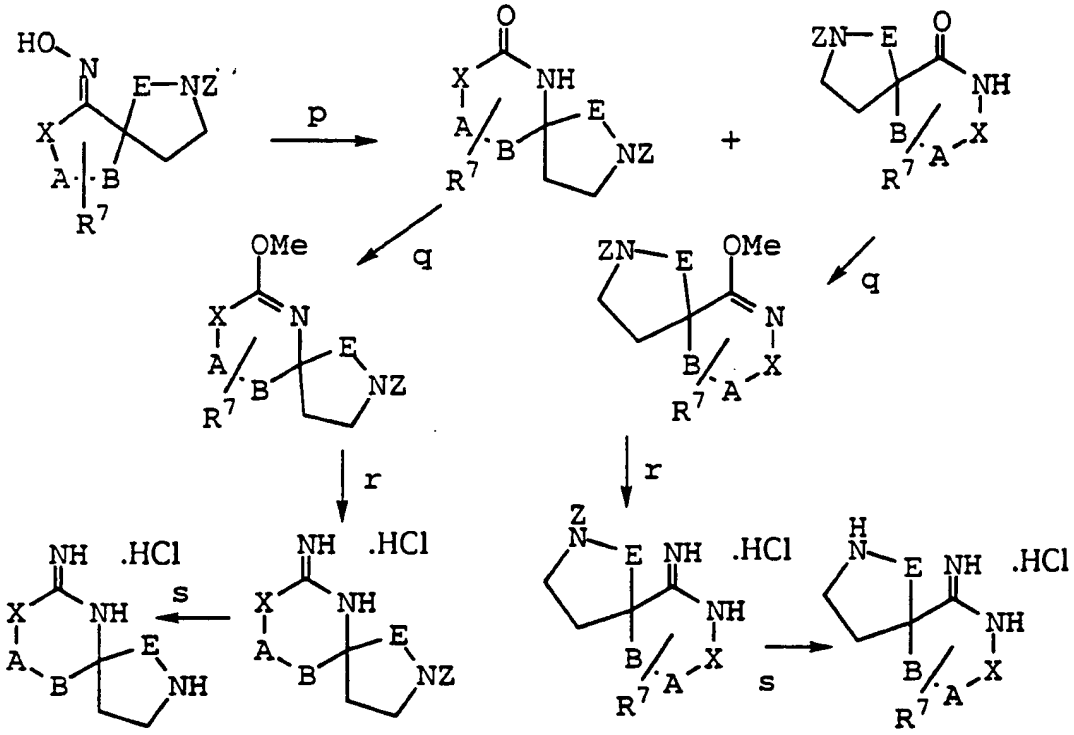


a) (t-butylOCO)$_2$O, DMAP, THF; b) LiHMDS, HMPA, THF, (1S)-(+)- (10-camphorsulfonyl)oxaziridine or (1R)-(-)-(10-camphorsulfonyl) oxaziridine; c) t-butyldimethylsilyl chloride, imidazole, DMF; d) $Mg(ClO_4)_2$ (20%), CH_3CN; e) Me_3O^+ BF_4^-, CH_2Cl_2; f) NH_4Cl, MeOH; g) (butyl)$_4N^+F^-$,MeOH; h) H_2, Pd/C.

Scheme 9:

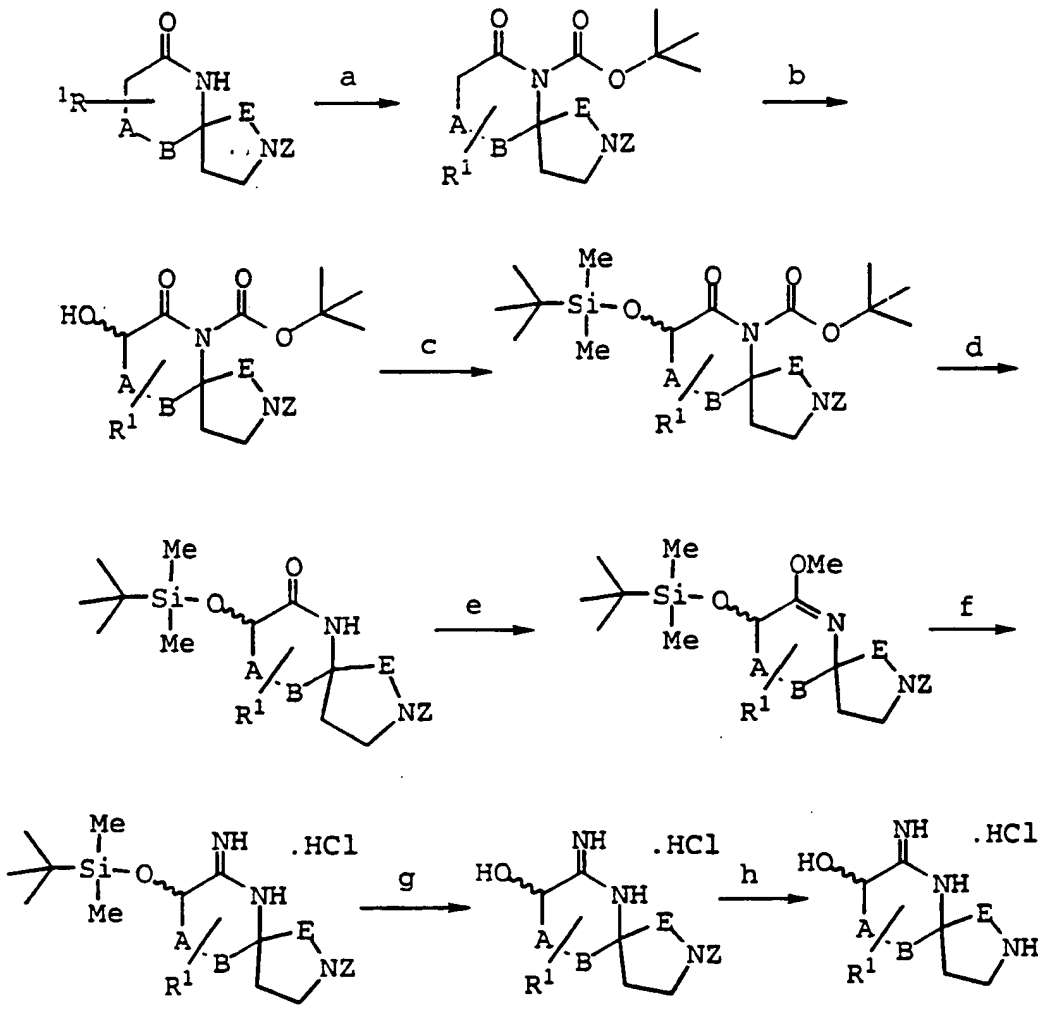

a, b
c
d
e
f
For E=CH2
a
For E=CH2CH2
g
h
i
j
k
For either E= CH2
or E= CH2CH2:
m
n

Scheme 9 (continued)



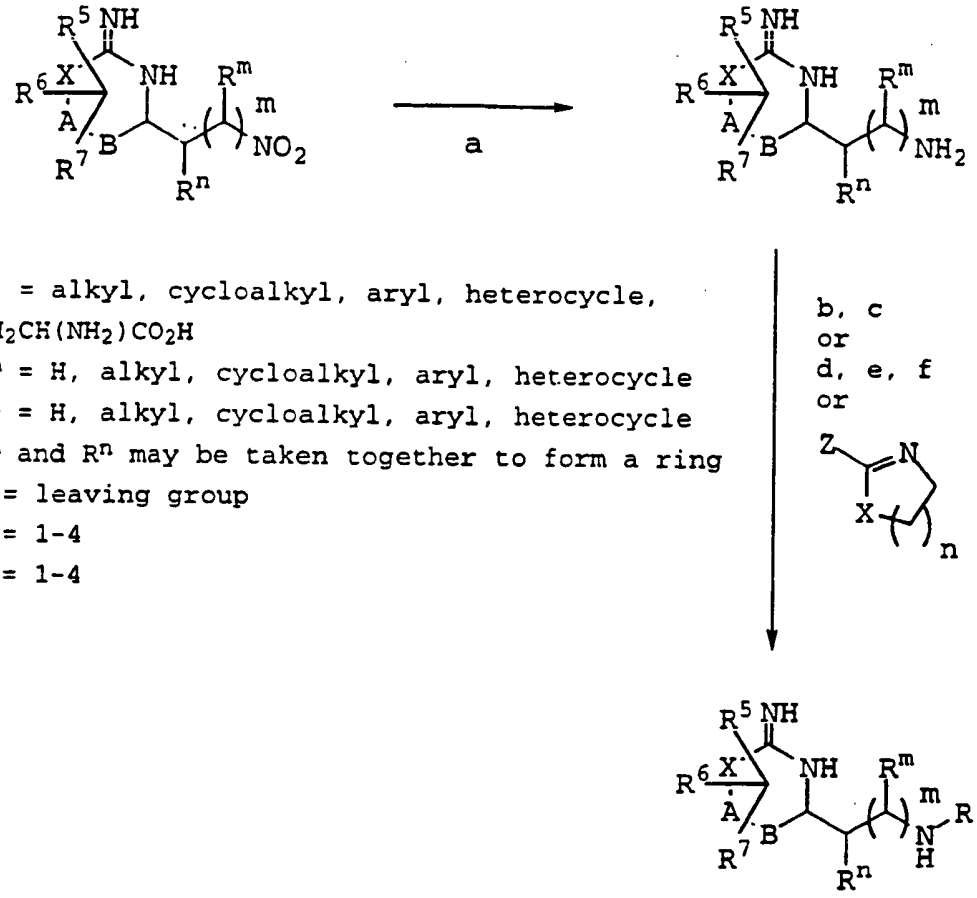
a) NaH/THF; b) $BrCH_2CN$/THF; c) Ethylene glycol/p-toluenesulfonic acid/toluene; d) $LiAlH_4/Et_2O$; e) Carbobenzoxy chloride/t-butanol/water/NaOH; f) p-Toluenesulfonyl chloride/CH_2Cl_2/pyridine; g) KCN/acetonitrile; h) KOH/ethylene glycol; i) MeI/DMF/$NaHCO_3$; j) H_2/Pd/MeOH; k) B_2H_6/THF; m) HCl/AcOH/H_2O; n) NH_2OH; p) Benzenesulfonyl chloride/H_2O/NaOH; q) Trimethyloxonium tetrafluoroborate; r) NH_4Cl/MeOH;s) H_2/Pd/C.

Scheme 10:



a) (t-butylOCO)$_2$O, DMAP, THF; b) LiHMDS, HMPA, THF, (1S)-(+)-(10-camphorsulfonyl)oxaziridine or (1R)-(-)-(10-camphorsulfonyl) oxaziridine; c) t-butyldimethylsilyl chloride, imidazole, DMF; d) Mg(ClO_4)2 (20%), CH_3CN; e) $Me_3O^-BF_4^-$, CH_2Cl_2; f) NH_4Cl, MeOH; g) (butyl)$_4N^-F^-$, MeOH; h) H_2, Pd/C.

Scheme 11:



R = alkyl, cycloalkyl, aryl, heterocycle, $CH_2CH(NH_2)CO_2H$
R^m = H, alkyl, cycloalkyl, aryl, heterocycle
R^n = H, alkyl, cycloalkyl, aryl, heterocycle
R^m and R^n may be taken together to form a ring
Z = leaving group
n = 1-4
m = 1-4

a) catalytic hydrogenation; b) RCHO; c) reduction;
d) $CH_2=C(NHZ)CO_2Me$; e) reduction; f) hydrolysis

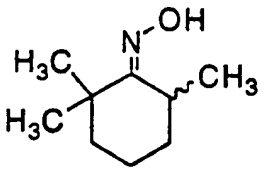
Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the following preferred specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

All experiments were performed under either dry nitrogen or argon. All solvents and reagents were used without further purification unless otherwise noted. The routine work-up of the reactions involved the addition of the reaction mixture to a mixture of either neutral, or acidic, or basic aqueous solutions and organic solvent. The aqueous layer was extracted

n times (x) with the indicated organic solvent. The combined organic extracts were washed n times (x) with the indicated aqueous solutions, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and purified as indicated. Separations by column chromatography were achieved with conditions described by Still. (Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatograhic Technique for Preparative Separation with Moderate Resolution. *J. Org. Chem.*, **1978**, *43*, 2923-2925.) The hydrochloride salts were made from 1N HCl, HCl in ethanol (EtOH), 2 N in MeOH, or 6 N HCl in dioxane. Thin layer chromatograms were run on 0.25 mm EM precoated plates of silica gel 60 F254. High performance liquid chromatograms (HPLC) were obtained from C-8 or C-18 reverse phase columns which were obtained from several vendors. Analytical samples were dried in an Abderhalden apparatus at either 56°C or 78°C. ^1H NMR spectra were obtained from either General Electric QE-300 or Varian VXR 400 MHz spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR were obtained from a Varian spectrometer at 125.8 MHz with tetramethylsilane as an internal standard.

Example 1

2,2,6-trimethylcyclohexanone, oxime



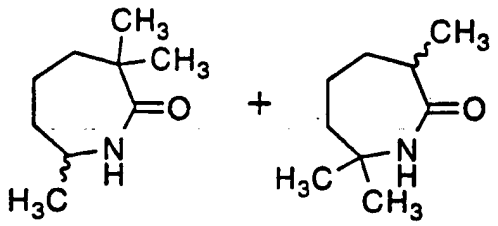
A Sample of 2,2,6-trimethylcyclohexanone (Aldrich, 4.9 g, 39.0 mmol) was combined with hydroxylamine hydrochloride (NH_2OH . HCl, 3.6 g, 52.4 mmol) and sodium acetate (NaOAc, 5.2 g, 62.9 mmol) in a mixture of ethanol (EtOH, 35 mL) and water (25 mL). This mixture was refluxed for 5 h under a nitrogen atmosphere. After the reaction was cooled to room temperature and stirred for an additional 5 days, all solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (EtOAc) and water and the organic phase was washed with 1 x 75 mL of saturated NaCl (brine), dried over Na_2SO_4, and stripped of all solvent under reduced pressure. This provided 5.0 g (91%) of the title compound as a white solid. This material showed a retention time of 9.6 min (100% purity by peak area integration) on a Shimadzu GC-14A gas chromatograph (GC) with a 0.25 mm x 25 M methyl, 5% phenylsilicone column using helium as the carrier gas and a temperature program starting at 55 °C and increasing 10 °/minute up to 200 °C. The NMR and IR spectra were also consistent with the assigned structure.

Elemental analysis: $C_9H_{17}NO \cdot 0.1\ H_2O$ (MW = 157.04)

	C	H	N
Calculated:	68.83	11.04	8.92
Found:	69.00	11.00	8.85

Example 2

Isomer-A: hexahydro-3,3,7-trimethyl-2H-azepin-2-one
Isomer-B: hexahydro-3,7,7-trimethyl-2H-azepin-2-one

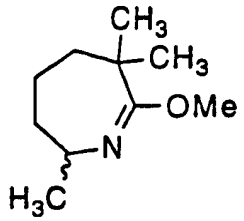


Isomer-A Isomer-B

A 4.9 g (34.3 mmol) sample of the title material of Example 1 was added to a dropping funnel containing 6 mL of 80% H_2SO_4. After using a stirring rod to obtain a turbid solution, this mixture was added dropwise (10 min) to 5 mL of 80% H_2SO_4 stirred magnetically and maintained at 120 °C with an external oil bath. Within 5 minutes of the start of addition an exotherm was noted and the temperature of the reaction rose to 160 °C before cooling again to 120 °C. Ten minutes later the flask was removed from the bath and allowed to cool to room temperature. The product mixture was diluted with water (20 mL) and brought to pH 6 with concentrated NH_4OH. This solution was further diluted with 75 mL of water and extracted with 3 x 75 mL of CH_2Cl_2. The combined organic phase was washed with 1 x 50 mL of brine, dried (Na_2SO_4), filtered, and stripped of all solvent under reduced pressure. The oily residue (2.9 g, 56%) is separated by HPLC on silica gel to yield the title products.

Example 3

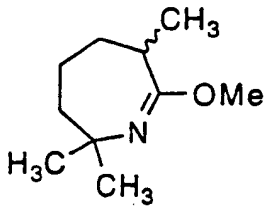
3,4,5,6-tetrahydro-7-methoxy-2,6,6-trimethyl-2H-azepine



To a magnetically stirred slurry of trimethyloxonium tetrafluoroborate (Lancaster, 0.30 g, 2.0 mmol) and 3A molecular sieves (2 g) in CH_2Cl_2 (15 mL) under argon (Ar) was added the Isomer-A product of Example 2 (0.31 g, 1.5 mmol). This mixture was stirred at room temperature for 3 days before it was diluted with 10 mL of CH_2Cl_2 and partitioned between 40 mL of saturated $KHCO_3$ and 50 mL of EtOAc. The organic phase was separated, dried over Na_2SO_4, filtered, and stripped of all solvent under reduced pressure to provide the crude title product as a pale yellow oil. This material was chromatographed on a short path Merck flash silica column eluting with EtOAc/n-hexane (1:1). The title pale yellow liquid product (308 mg, 93%) had a GC retention time of 15.5 min (100%) under the conditions of Example 1 and NMR and IR spectra consistent with the indicated product.

Example 4

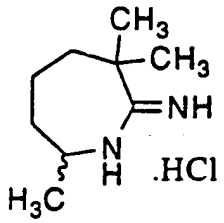
3,4,5,6-tetrahydro-7-methoxy-2,2,6-trimethyl-2H-azepine



The Isomer-B product of Example 2 is reacted with trimethyloxonium tetrafluoroborate by the method of Example 3 to produce the title material.

Example 5

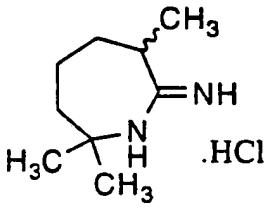
hexahydro-3,3,7-trimethyl-2H-azepin-2-imine, monohydrochloride



The title product of Example 3 (0.30 g, 1.4 mmol) and 0.06 g (1.1 mmol) of ammonium chloride (NH_4Cl) were refluxed in 13 mL of methanol (MeOH) under a nitrogen atmosphere for 19 h. After cooling the reaction to room temperature, it was filtered, stripped of all solvent under reduced pressure, and partitioned between 15 mL of water and 7 mL of CH_2Cl_2. The organic and aqueous phases were separated and the aqueous phase was washed with a 25 mL portion of EtOAc before it was lyophilized to provide 0.24 g (92%) of the white solid title material.

Example 6

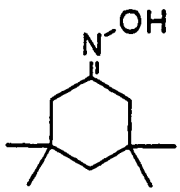
hexahydro-3,7,7-trimethyl-2H-azepin-2-imine, monohydrochloride



The product of Example 4 in MeOH is reacted with ammonium chloride by the method of Example 5 to generate the title material.

Example 7

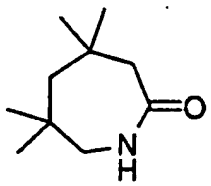
3,3,5,5-tetramethylcyclohexanone, oxime



A sample of 3,3,5,5-tetramethylcyclohexanone (Aldrich, 6.2 g, 40.0 mmol) was converted to the title compound by the method of Example 1 using 5.6 g (80.0 mmol) of hydroxylamine hydrochloride and 6.7 g (82.0 mmol) of NaOAc in a mixture of 60 mL of EtOH and 60 mL of water. The procedure produced 7.5 g (100%) of the title material as a white solid.

Example 8

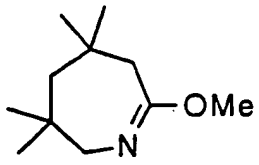
hexahydro-4,4,6,6-tetramethyl-2H-azepin-2-one



A sample of the product of Example 7 (7.5 g, 44.4 mmol) was converted to the title compound by the method of Example 2 using 11 mL of 80% H_2SO_4. The procedure produced 5.6 g (75%) of the title material as a pale yellow tacky solid.

Example 9

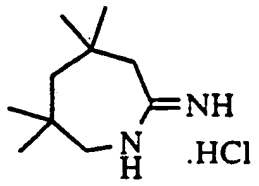
3,4,5,6-tetrahydro-7-methoxy-3,3,5,5-tetramethyl-2H-azepine



The title product of Example 8 (845 mg, 5.0 mmol) was reacted with trimethyloxonium tetrafluoroborate (962 mg, 5.0 mmol) by the method of Example 3 to yield 815 mg (100%) of the title material.

Example 10

hexahydro-4,4,6,6-tetramethyl-2H-azepin-2-imine, monohydrochloride



The product of Example 9 (110 mg, 0.6 mmol) in 3.5 mL of MeOH was reacted with ammonium chloride (32 mg, 0.6 mmol) by the method of Example 5 to yield 90 mg (67%) of the title material.

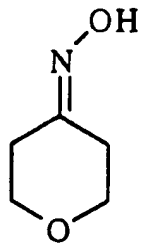
HRMS (EI) calcd for $C_{10}H_{20}N_2$ m/e 168.163, found m/e 168.162.
^1H NMR(CD_3OD): δ 3.21 (s, 2H), 2.62 (s, 2H), 1.54 (s, 2H), 1.1 (s, 6H), 1.01 (s, 6H).

Elemental analysis: $C_{10}H_{20}N_2 \cdot HCl \cdot 0.3\ H_2O \cdot 0.25\ NH_4Cl$ (MW = 223.52)

	C	H	N	Cl
Calculated:	53.74	10.19	14.10	19.83
Found:	53.71	9.66	13.99	19.59

Example 11

Tetrahydro-4H-pyran-4-one, oxime

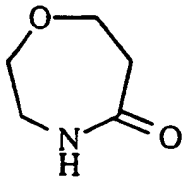


Tetrahydro-4H-pyran-4-one (5.0 g, 0.05 mole), hydroxylamine hydrochloride (5.2 g, 0.075 mole) and sodium acetate (13.6 g, 0.1 mole) were refluxed in ethanol (30 mL)/H_2O (20 mL) overnight. Contents were allowed to cool and concentrated in vacuo to remove the ethanol. The aqueous solution left was extracted with CH_2Cl_2 which was dried ($MgSO_4$) and concentrated in vacuo leaving the title material as a white solid (5.4 g).

1H NMR ($CDCl_3$): δ 9.15 (br, 1H); 3.85-3.70 (m, 4H); 2.72 - 2.60 (m, 2H); 2.40 - 2.35 (m, 2H).

Example 12

tetrahydro-1,4-oxazepin-5(2H)-one



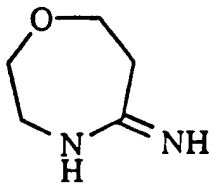
To the title material of Example 11 (5.4 g, 0.047 mole) in acetone (30 mL) at 0 °C was added 1N sodium hydroxide. Benzene sulfonyl chloride (6 mL, 0.047 mole) in acetone (10 mL) was added dropwise with magnetic stirring. Contents were stirred [illegible] hours and concentrated in vacuo to remove the acetone. The aqueous solution was extracted with CH_2Cl_2 (2 x 150 mL), dried ($MgSO_4$) and concentrated in vacuo leaving an amber oil/solid

(2.2 g). The residue was crystallized from hexanes to give the title material as a white solid (1.37 g).

1H NMR ($CDCl_3$): δ 6.90 (br, 1H); 3.82 - 3.70 (m, 4H); 3.38 - 3.30 (m, 2H); 2.75 - 2.65 (m, 2H).

Example 13

tetrahydro-1,4-oxazepin-5(2H)-imine, trifluoroacetate salt



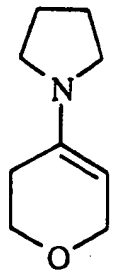
• TFA

The title material of Example 12 (960 mg, 0.008 mole) and trimethyloxonium tetrafluoroborate (1.5 g, 0.01 mole) were mixed in CH_2Cl_2 (50 mL) and stirred 72 hours. Contents were concentrated in vacuo and the residue was dissolved in methanol (50 mL). Anhydrous ammonia was bubbled through for 15 minutes. Contents were stoppered and stirred overnight. After concentrating in vacuo, the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was purified by C-18 reverse phase chromatography eluting with 100% H_2O (0.05% TFA) to give the title material as a white solid (730 mg).

1H NMR (D_2O): δ 3.78 - 3.72 (m, 2H); 3.68 - 3.63 (m, 2H); 3.49 - 3.44 (m, 2H); 2.85 - 2.80 (m, 2H).

Example 14

1-(5,6-dihydro-2H-pyran-4-yl)pyrrolidine

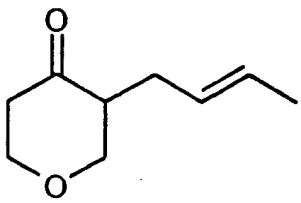


Tetrahydro-4H-pyran-4-one (5.0 g, 0.05 mole) and pyrrolidine (4.6 mL, 0.055 mole) were refluxed in benzene (50 mL) with a Dean Stark trap to collect water for 2 hours. Contents were concentrated in vacuo leaving a thick amber oil (7.6 g) which was distilled on a kugelrohr apparatus at 40 °C (0.1 mm) to give the title material as a clear colorless oil (5.9 g).

1H NMR ($CDCl_3$): δ 4.28 - 4.20 (m, 2H); 4.20 - 4.13 (m, 1H); 3.88 - 3.78 (m, 2H); 3.07 - 2.95 (m, 4H); 2.35 - 2.22 (m, 2H); 1.90 - 1.80 (m, 4H).

Example 15

3-(2-Butenyl)tetrahydro-4H-pyran-4-one



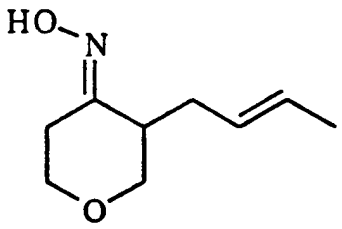
The title material of Example 14 (23 g, 0.15 mole) and crotyl bromide (15.4 mL, 0.15 mole) were mixed in benzene (200 mL) and stirred 72 hours. Water (50 mL) was added and stirred 2 hours. The benzene layer was removed and the aqueous layer was extracted with EtOAc (150 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated in vacuo leaving an oil

(20.8 g). The oil was chromatographed on silica gel eluting with 5% EtOAc/hexanes to give the title material as a colorless oil (12.3 g).

1H NMR ($CDCl_3$): δ 5.52 - 5.25 (m, 2H); 4.20 - 4.07 (m, 2H); 3.82 - 3.70 (m, 1H); 3.50 - 3.40 (m, 1H); 2.68 - 2.40 (m, 4H); 2.03 - 1.90 (m, 1H); 1.65 (d, J = 6 Hz, 3H).

Example 16

3-(2-Butenyl)tetrahydro-4H-pyran-4-one, oxime

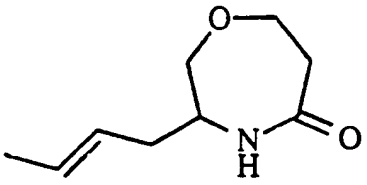


To the title material of Example 15 (13.0 g, 0.084 mole) and hydroxylamine hydrochloride (6.5 g, 0.093 mole) in methanol (100 mL) was added dropwise anhydrous pyridine (8.1 mL, 0.1 mole) in methanol (50 mL). Contents were stirred overnight. Contents were concentrated in vacuo and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated in vacuo leaving the title material as an oil (19.5 g).

1H NMR ($CDCl_3$) as a mixture of syn and anti oximes: δ [9.0, 8.85 (br, 1H)]; [5.80 - 5.25, 5.20 - 4.85 (m, 2H)]; 4.20 - 2.90 (m, 5H); 2.80 - 2.00 (m, 4H); [1.63 (d, J = 6 Hz), 1.20 - 0.90 (m) (3H)].

Example 17

3-(2-Butenyl)tetrahydro-1,4-oxazepin-5(2H)-one

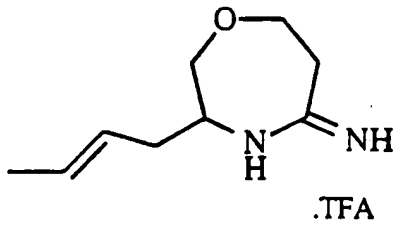


To the title material of Example 16 (5.0 g, 0.03 mole) in acetone (30 mL) at 0 °C was added 1N sodium hydroxide (30 mL). Benzene sulfonyl chloride (3.8 mL, 0.03 mole) in acetone (10 mL) was added dropwise and after the reaction came, to room temperature, it was stirred overnight. The contents were concentrated in vacuo to remove acetone and the aqueous solution left was extracted with CH_2Cl_2 (2 x 150 mL). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and concentrated in vacuo leaving an oil. Hexane was added to the oil, the resulting white solid was filtered and recrystallized from EtOAc/hexane to give the title material as a white solid (812 mg). From the mother liquor was isolated additional title material plus its other regeoisomer, 6-(2-Butenyl)tetrahydro-1,4-oxazepin-5(2H)-one, which was separated by chromatography.

1H NMR ($CDCl_3$): δ 5.75 (br, 1H); 5.70 - 5.50 (m, 1H); 5.40 - 5.23 (m, 1H); 4.00 - 3.80 (m, 2H); 3.72 - 3.52 (m, 2H); 3.40 - 3.30 (m, 1H); 2.95 - 2.80 (m, 1H); 2.60 - 2.55 (m, 1H); 2.30 - 2.15 (m, 1H); 2.10 - 1.95 (m, 1H); 1.70 (d, J = 6 Hz, 3H).

Example 18

3-(2-Butenyl)tetrahydro-1,4-oxazepin-5(2H)-imine, trifluoroacetate salt



.TFA

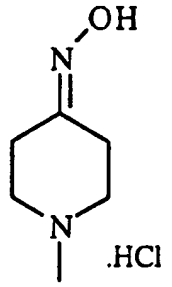
To the title material of Example 17 (612 mg, 3.6 mmol) in CH_2Cl_2 (25 mL) was added trimethyloxonium tetrafluoroborate (540 mg, 3.6 mmol) and contents were stirred overnight. After concentrating in vacuo, the residue was dissolved in methanol (25 mL) and anhydrous ammonia was bubbled through the solution. Contents were stoppered and stirred 72 hours. Contents were concentrated in vacuo and the residue was purified by C-18 reverse phase chromatography eluting with a CH_3CN/H_2O gradient (0.05 % TFA) to give the title material as a white solid (404 mg).

Mass spectral analysis for $C_9H_{16}N_2O$: M^+H = 169.

1H NMR ($CDCl_3$): δ 9.7 (br, 2H); 8.9 (br, 1H); 5.70 - 5.54 (m, 1H); 5.40 - 5.25 (m, 1H); 4.03 - 3.92 (m, 1H); 3.90 - 3.80 (m, 1H); 3.76 - 3.58 (m, 2H); 3.46 - 3.32 (m, 1H); 3.04 - 2.76 (m, 2H); 2.42 - 2.18 (m, 2H); 1.67 (d, J = 6 Hz, 3H).

Example 19

1-Methyl-4-piperidin-4-one, oxime, monohydrochloride

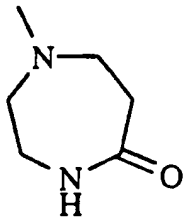


To a slurry of 1-methyl-4-pyridone (10 mL, 0.08 mole) and hydroxylamine hydrochloride (6.1 g, 0.088 mole) in methanol (100 mL) was added anhydrous pyridine (7.8 mL, 0.097 mole) in methanol (50 mL) dropwise. Contents were stirred overnight and the title material was filtered as a white solid (9.2 g). More of the title material was recovered from the methanol filtrate (7.7 g).

1H NMR (D_2O): δ 3.70 - 2.90 (m, 5H); 2.80 (s, 3H); 2.60 - 2. 45 (m, 2H); 2.40 - 2.10 (m, 1H).

Example 20

hexahydro-1-methyl-5H-1,4-diazepin-5-one



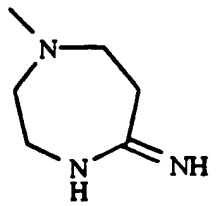
To the title material of Example 19 (9.2 g, 0.056 mole) in acetone (50 mL) at 0 °C was added dropwise 1N sodium hydroxide. After stirring 5 minutes, benzene sulfonyl chloride (7.1 mL) in acetone (5 mL) was added dropwise. Contents were stirred 72 hours, coming to room temperature. Contents were concentrated

in vacuo to remove the acetone, the aqueous solution was made basic with 1N sodium hydroxide and lyophilized leaving a solid. The solid was triturated with CH_2Cl_2 and filtered. The CH_2Cl_2 was concentrated in vacuo leaving the title material as a solid (4.9 g).

1H NMR ($CDCl_3$): δ 6.85 (br, 1H); 3.30 - 3.20 (m, 2H); 2.65 - 2.40 (m, 6H); 2.35 (s, 3H).

Example 21

hexahydro-1-methyl-5H-1,4-diazepin-5-imine, trifluoroacetate salt



.TFA

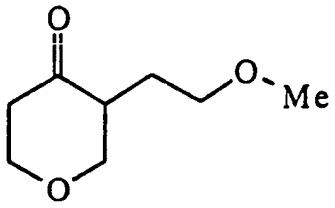
The 5-Oxo-2,3,4,5,6,7-hexahydro-1,4-diazepine product of Example 20 was treated with $Me_3O^+BF_4^-$ in CH_2Cl_2 and stirred overnight. After concentrating in vacuo, the residue was dissolved in methanol and anhydrous ammonia was bubbled through the solution. The contents were stirred overnight and concentrated in vacuo. The residue was purified by C-18 reverse phase chromatography to give the title product.

Mass spectral analysis for $C_6H_{13}N_3$: M^+H = 128.

^1H NMR (DMSO-d6): δ 9.80 - 9.40 (s, 1H); 9.40 (s, 1H); 9.10 (s, 1H); 8.60 (s, 1H); 3.70 - 2.85 (m, 8H); 2.80 (s, 3H).

Example 22

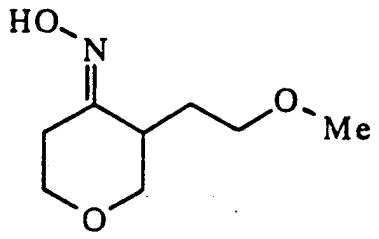
tetrahydro-3-(2-methoxyethyl)-4H-pyran-4-one



The title compound of Example 14 is reacted with bromoethyl methyl ether by the method of Example 15 to generate the title compound.

Example 23

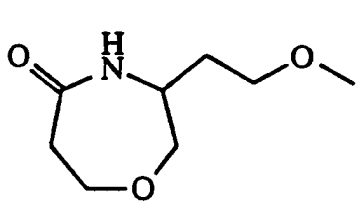
tetrahydro-3-(2-methoxyethyl)-4H-pyran-4-one, oxime



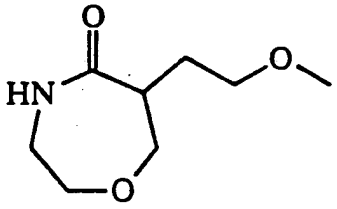
The title compound of Example 22 is reacted with hydroxylamine by the method of Example 16 to generate the title compound.

Example 24

Isomer-A: tetrahydro-3-(2-methoxyethyl)-1,4-oxazepin-5(2H)-one
Isomer-B: tetrahydro-6-(2-methoxyethyl)-1,4-oxazepin-5(2H)-one



Isomer A

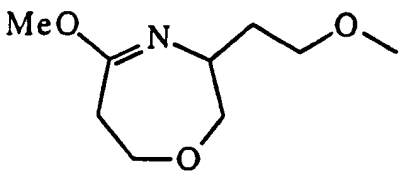


Isomer B

The title compound of Example 23 is reacted with benzenesulfonyl chloride by the method of Example 17 to generate the title compounds. The isomers are separated by column chromatography.

Example 25

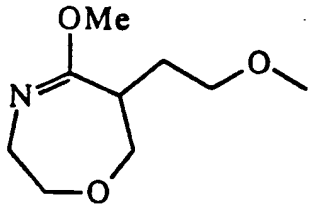
2,3,6,7-tetrahydro-3-(2-methoxyethyl)-5-methoxy-1,4-oxazepine



The Isomer A of Example 24 is reacted with trimethyloxonium tetrafluoroborate in methylene chloride by the method of Example 3 to generate the title compound.

Example 26

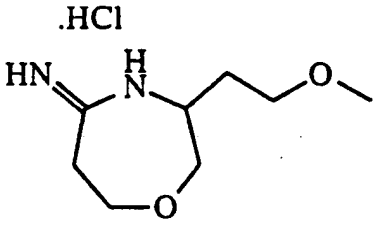
2,3,6,7-tetrahydro-6-(2-methoxyethyl)-5-methoxy-1,4-oxazepine



The isomer B of Example 24 is reacted with trimethyloxonium tetrafluoroborate in methylene chloride by the method of Example 3 to generate the title compound.

Example 27

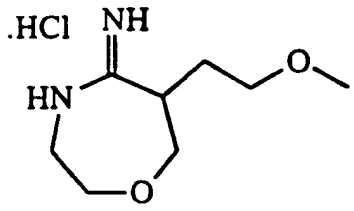
tetrahydro-3-(2-methoxyethyl)-1,4-oxazepin-5(2H)-imine, monohydrochloride



The product of Example 25 is reacted with ammonium chloride in methanol by the method of Example 4 to generate the title compound.

Example 28

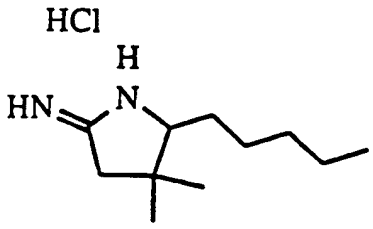
tetrahydro-6-(2-methoxyethyl)-1,4-oxazepin-5(2H)-imine, monohydrochloride



The product of Example 26 is reacted with ammonium chloride in methanol by the method of Example 4 to generate the title compound.

Example 29

4,4-dimethyl-5-pentylpyrrolidin-2-imine, monohydrochloride



Example 29A) Ethyl 3,3-dimethylacrylate (4.9 g, 38 mmol) was mixed with nitrohexane (5.0 g, 38 mmol), 1M tetrabutylammoniumfluoride (in THF, 38 mL) and heated at 40 °C for 24 hours. The reaction mixture was diluted with diethyl ether, washed with brine, followed by water. Purification by chromatography on silica gel yielded the product, methyl 3,3-dimethyl-4-nitrononanoate (6.6 g, 67%).

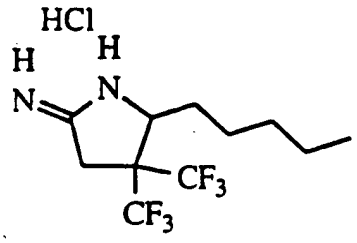
Example 29 B) The product of Example 29 A (5.6 g, 24 mmol) in absolute MeOH was hydrogenated over RaNi at 55 °C and 60 psi for 24h. The reaction product was purified by column chromatography to yield 4,4-dimethyl-5-pentylpyrrolidin-2-one (2.63 g, 60%).

Example 29 C) The product of Example 29 B (2.63 g, 14.3 mmol) was treated with trimethyloxonium tetrafluoroborate (2.56 g, 17.4 mmol) in DCM (20 mL) by the method of Example 3, to yield 3,4-dihydro-5-methoxy-3,3-dimethyl-2-pentyl-2H-pyrrole (2.0 g, 71%).

Example 29) A solution of the title product of Example 29 C (2.0 g, 10 mmol) in MeOH (30 mL) was reacted with ammonium chloride (529 mg, 9.9 mmol) by the method of Example 5 followed by chromatography on reverse phase HPLC.

Example 30

5-pentyl-4,4-bis(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride



Example 30 A) Ethyl 4,4,4-trifluoro-3-(trifluromethyl)crotonate (9.0 g, 38 mmol) was mixed with nitrohexane (5.0 g, 38 mmol), potassium carbonate (5.3 g, 38 mmol) and Aliquat 336 (20 drops). The mixture was sonicated at room temperature. When the reaction, monitored by G.C., was complete the mixture was acidified with HCl (1 N) and the aqueous phase extracted with ether. Purification by chromatography on silica gel yielded the product, methyl 4-nitro-3,3-bis(trifluoromethyl)nonanoate (3 g, 21%).

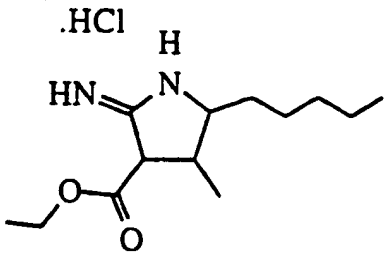
Example 30 B) The product of Example 30 A in absolute MeOH is hydrogenated over RaNi at 55°C and 60 psi for 24h. The reaction product is purified by column chromatography to yield 5-pentyl-4,4-bis(trifluoromethyl)pyrrolidin-2-one.

Example 30 C) The product of Example 30 B is treated with trimethyloxonium tetrafluoroborate in DCM (20 mL) by the method of Example 3, to yield 3,4-dihydro-5-methoxy-2-pentyl-3,3-bis(trifluoromethyl)-2H-pyrrole.

Example 30) A solution of the title product of Example 30 C in MeOH (30 mL) is reacted with ammonium chloride by the method of Example 5 followed by chromatography on reverse phase HPLC to generate the title material.

Example 31

ethyl 2-imino-4-methyl-5-pentylpyrrolidine-3-carboxylate, monohydrochloride



Example 31 A) The diethyl ethylidenemalonate (6.4 g, 33 mmol) is mixed with nitrohexane (5 g, 38 mmol), potassium carbonate (2 g) and Aliquat 336 (10 drops). The mixture is sonicated at room temperature. When the reaction, monitored by G.C., is complete the mixture is acidified with HCl (1 N) and the aqueous phase extracted with ether. Purification by chromatography on silica gel yields the product, diethyl 2-(1-methyl-2-nitroheptyl)propane-1,3-dioate.

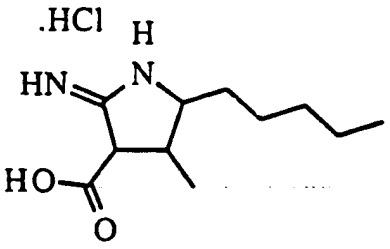
Example 31 B) The product of Example 31 A in absolute EtOH is hydrogenated over RaNi at 55 °C and 60 psi for 24h. The reaction product is purified by column chromatography to yield ethyl 4-methyl-2-oxo-5-pentylpyrrolidine-3-carboxylate.

Example 31 C) The material 31 B is treated with trimethyloxonium tetrafluoroborate in DCM by the method of Example 3, to yield ethyl 3,4-dihydro-5-methoxy-2-pentyl-2H-pyrrole-3-carboxylate.

Example 31) A solution of the title product of Example 31 C in MeOH is reacted with ammonium chloride by the method of Example 5 followed by chromatography on reverse phase HPLC to generate title material.

Example 32

2-imino-4-methyl-5-pentylpyrrolidine-3-carboxylic acid, monohydrochloride



Example 32 A) A solution of the title product of Example 31 B in MeOH / 2N NaOH is stirred 6h followed by lyophilization. The resulting solid is dissolved in water and EtOAc containing benzylbromide added. The mixture is shaken in a separatory funnel. The organic solution is separated, dried and evaporated. The residue is purified by column chromatography to yield phenylmethyl 4-methyl-2-oxo-5-pentylpyrrolidine-3-carboxylate.

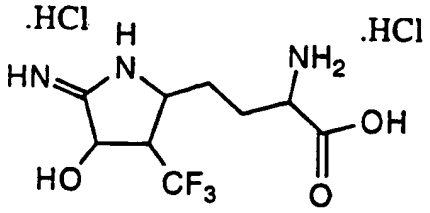
Example 32 B) The product of Example 32 A is treated with trimethyloxonium tetrafluoroborate in DCM by the method of Example 3, to yield phenylmethyl 3,4-dihydro-5-methoxy-3-methyl-2-pentyl-2H-pyrrole-4-carboxylate.

Example 32 C) A solution of the title product of Example 32 B in MeOH is reacted with ammonium chloride by the method of Example 5 followed by chromatography on reverse phase HPLC to generate phenylmethyl 2-imino-4-methyl-5-pentyl-3-carboxylate.

Example 32) A solution of product of Example 32 C in absolute MeOH is hydrogenated over Pd/C. The reaction product is purified by chromatography on reverse phase HPLC to generate title material.

Example 33

α-amino-4-hydroxy-5-imino-3-(trifluoromethyl)pyrrolidine-2-butanoic acid, monohydrochloride



Example 33 A) The ethyl 4,4,4-trifluoromethyl crotonate (10 mmol) and 2-(2-nitroethyl)-1,3-dioxolane (12 mmol) are reacted with, potassium carbonate (5 mmol) and Aliquat 336 (3 drops), by the method of Example 14. Purification by chromatography on silica gel yields ethyl γ-nitro-β-(trifluoromethyl)-1,3-dioxolane-2-pentanoate.

Example 33 B) The product of Example 33 A in MeOH is hydrogenated over RaNi at 55°C and 60 psi for 6h. The reaction product is purified by column chromatography to yield 5-[(1,3-dioxolan-2-yl)methyl]-4-(trifluoromethyl)pyrrolidin-2-one as a mixture of diasteromers.

Example 33 C) The product of Example 33 B is treated with di-t-butyldicarbonate and DMAP in THF and refluxed for 2 h. The solvent is removed and the product is purified by column chromatography to yield 1,1-dimethylethyl 2-[(1,3-dioxolan-2-yl)methyl]-5-oxo-3-(trifluoromethyl)pyrrolidine-1-carboxylate.

Example 33 D) The product of Example 33 C with HMPA (1 equivalent) in THF at -70 °C is treated with Lithium hexamethyl disilazide (1.2 equivalents, 1M in THF). The solution is allowed to warm to -40 °C then cooled to -70 °C, and a solution of camphor sulfonyl oxaziridine in THF is added. The solution is stirred at -40 °C for 2h then quenched onto saturated NH_4Cl. The solution is then extracted with EtOAc. The organics are combined. The solvent is removed and the product is purified by column chromatography to yield 1,1-dimethylethyl 2-[(1,3-dioxolan-2-yl)methyl]-4-hydroxy-5-oxo-3-(trifluoromethyl)pyrrolidine-1-carboxylate.

Example 33 E) The product of Example 33 D is treated with NaH and benzylbromide in THF. The product is purified by column chromatography to yield 1,1-dimethylethyl 2-[(1,3-dioxolan-2-yl)methyl]-5-oxo-4-(phenylmethoxy)-3-(trifluoromethyl)pyrrolidine-1-carboxylate.

Example 33 F) The product of Example 33 E in MeOH is treated with HCl (1N) to yield 5-oxo-4-(phenylmethoxy)-3-(trifluoromethyl)pyrrolidine-2-acetaldehyde which is used directly in the next step.

Example 33 G) To a solution of product of Example 33 F and Z-α-phosphonoglycine trimethyl ester in CH_2Cl_2 is added DBU. The solution is stirred for 2h The solvent is removed and the product is purified by column chromatography to yield methyl 4-[5-oxo-4-(phenylmethoxy)-3-(trifluoromethyl)pyrrolidin-2-yl]-2-[[(phenylmethoxy)carbonyl]amino]-2-butenoate.

Example 33 H) The product of Example 33 G is hydrogenated with $[Rh(COD)(R,R\text{-DIPAMP})]^+ BF_4^-$. The solvent is removed and the product is purified by column chromatography to yield methyl 5-oxo-α-[[(phenylmethoxy)carbonyl]amino]-4-(phenylmethoxy)-3-(trifluoromethyl)pyrrolidine-2-butanoate.

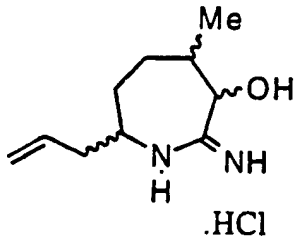
Example 33 I) The product of Example 33 H is treated with trimethyloxonium tetrafluoroborate in DCM by the method of Example 3, to yield methyl 3,4-dihydro-5-methoxy-α-[[(phenylmethoxy)carbonyl]amino]-4-(phenylmethoxy)-3-(trifluoromethyl)-2H-pyrrole-2-butanoate.

Example 33 J) A solution of the title product of Example 33 I in MeOH is reacted with ammonium chloride by the method of Example 5 followed by chromatography on reverse phase HPLC to yield methyl 5-imino-α-[[(phenylmethoxy)carbonyl]amino]-4-(phenylmethoxy)-3-(trifluoromethyl)pyrrolidine-2-butanoate, monohydrochloride.

Example 33) The product of Example 33 J in absolute MeOH is hydrogenated over Pd/C for 24h. The reaction product is purified by chromatography on reverse phase HPLC to yield 33.

Example 34

hexahydro-2-imino-4-methyl-7-(2-propenyl)-1H-azepin-3-ol



Example 34 A) A THF solution of hexahydro-4-methyl-7-(2-propenyl)-2H-azepin-2-one is treated with di-t-butyldicarbonate and dimethylaminopyridine (DMAP, 1 eq) to generate the Boc protected lactam, 1,1-dimethylethyl hexahydro-4-methyl-2-oxo-7-(2-propenyl)-1H-azepine-1-carboxylate.

Example 34B) To the product of Example 34 A above dissolved in THF and cooled to a low temperature is added hexamethylphosphoramide (HMPA, 1 eq) followed by lithium hexamethyldisilylazide (LHMDS, 1.1 eq). To this is added 1.2 equivalents of either (1S)-(+)-(camphorsulfonyl)-oxaziridine or (1R)-(-)-(camphorsulfonyl)-oxaziridine to generate a chromatographically separable mixture of diastereomers Isomer-A 1,1-dimethylethyl hexahydro-3R-hydroxy-4-methyl-2-oxo-7-(2-propenyl)-1H-azepine-1-carboxylate or Isomer-B 1,1-dimethylethyl hexahydro-3S-hydroxy-4-methyl-2-oxo-7-(2-propenyl)-1H-azepine-1-carboxylate.

Example 34 C) A product or product mixture from Example 34 B above dissolved in DMF is treated with imidazole (2 eq) and t-butyldimethylsilyl chloride yielding 1,1-dimethylethyl 3-[(1,1-dimethylethyl)dimethylsilyloxy]hexahydro-4-methyl-2-oxo-7-(2-propenyl)-1H-azepine-1-carboxylate.

Example 34 D) To a product or product mixture from Example 34 C above dissolved in acetonitrile and warmed to around 50 °C is added magnesium perchlorate [$Mg(ClO_4)_2$, 0.2 eq] generating 3-[(1,1-dimethylethyl)dimethylsilyloxy]hexahydro-4-methyl-2-oxo-7-(2-propenyl)-2H-azepin-2-one.

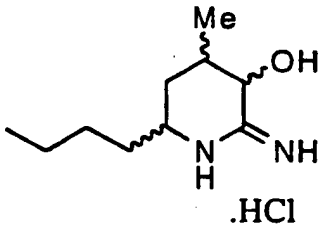
Example 34 E) The product or a product mixture from Example 34 D above is treated with trimethyloxonium tetrafluoroborate in CH_2Cl_2

by the method of Example 3, to yield 6-[(1,1-dimethylethyl)dimethylsilyloxy]-3,4,5,6-tetrahydro-7-methoxy-5-methyl-2H-azepine.

Example 34 F) A solution of the title product or a product mixture of Example 34 E in MeOH is reacted with ammonium chloride by the method of Example 5 to generate 3-[(1,1-dimethylethyl)dimethylsilyloxy]hexahydro-4-methyl-7-(2-propenyl)-2H-azepin-2-imine, monohydrochloride. This material is treated with a source of fluoride ion and the crude product chromatographed on reverse phase HPLC to yield the title material.

Example 35

6-butyl-3-hydroxy-4-methylpiperidin-2-imine, monohydrochloride



Example 35 A) A THF solution of 6-butyl-4-methylpiperidin-2-one is treated with di-t-butyldicarbonate and dimethylaminopyridine (DMAP, 1 eq) to generate the Boc protected lactam, 1,1-dimethylethyl 2-butyl-4-methyl-6-oxopiperidine-1-carboxylate.

Example 35 B) To the product of Example 35 A above dissolved in THF and cooled to a low temperature is added hexamethylphosphoramide (HMPA, 1 eq) followed by lithium hexamethyldisilylazide (LHMDS, 1.1 eq). To this is added 1.2 equivalents of either (1S)-(+)-(camphorsulfonyl)-oxaziridine or (1R)-(-)-(camphorsulfonyl)-oxaziridine to generate chromatographically separable mixture of diastereomers Isomer-A 1,1-dimethylethyl 6-butyl-3R-hydroxy-4-methyl-2-oxopiperidine-1-carboxylate or Isomer-B 1,1-dimethylethyl 6-butyl-3S-hydroxy-4-methyl-2-oxopiperidine-1-carboxylate.

Example 35 C) A product or product mixture from Example 35 B above dissolved in DMF is treated with imidazole (2 eq) and t-butyldimethylsilyl chloride yielding 1,1-dimethylethyl 6-butyl-

3-[(1,1-dimethylethyl)dimethylsilyloxy]-4-methyl-2-oxopiperidine-1-carboxylate.

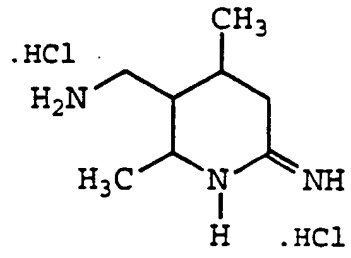
Example 35 D) To a product or product mixture from Example 35 C above dissolved in acetonitrile and warmed to around 50 °C is added magnesium perchlorate [$Mg(ClO_4)_2$, 0.2 eq] generating 6-butyl-3-[(1,1-dimethylethyl)dimethylsilyloxy]-4-methylpiperidin-2-one.

Example 35 E) The product or a product mixture from Example 35 D above is treated with trimethyloxonium tetrafluoroborate in CH_2Cl_2 by the method of Example 3, to yield 2-butyl-5-[(1,1-dimethylethyl)dimethylsilyloxy]-6-ethoxy-2,3,4,5-tetrahydro-4-methylpyridine.

Example 35 F) A solution of the title product or a product mixture of Example 35 E in MeOH is reacted with ammonium chloride by the method of Example 5 to generate 6-butyl-3-[(1,1-dimethylethyl)dimethylsilyloxy]-4-methylpiperidin-2-imine. This material is treated with a source of fluoride ion and the crude product chromatographed on reverse phase HPLC to yield the title material.

Example 36

6-imino-2,4-dimethylpiperidine-3-methanamine, dihydrochloride



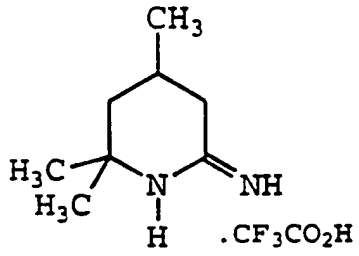
6-amino-2,4-dimethylpyridine-3-carbonitrile (1.5 g) and platinum oxide (500 mg) in ethanol (30 mL) and conc HCl (1 mL) were shaken on a Parr hydrogenation apparatus at 55 psi of hydrogen at 55 °C for 48 hours. The contents were filtered and the filtrate concentrated in vacuo leaving a waxy solid. Trituration with ethanol gave the title material as a white solid (191 mg).

Mass spectral analysis for $C_8H_{17}N_3$: M^+H = 156.

^1H NMR (D_2O): δ 3.63 - 3.40 (m, 2H); 3.20 - 3.07 (m, 1H); 2.72 - 2.60 (m, 1H); 2.40 - 2.25 (m, 1H); 2.05 - 1.90 (m, 2H); 1.25 (d, J = 6 Hz, 3H); 1.00 (d, J = 6 Hz, 3H).

Example 37

4,6,6-trimethylpiperidine-2-imine, trifluoroacetate salt



Example 37 A) A solution of 2,2,4-trimethylcyclopentanone (5.5 g, 44 mmol) in 35 mL EtOAc/25 mL of water was refluxed with hydroxylamine hydrochloride (4.6 g, 66 mmoles) and sodium acetate trihydrate (10.8 g, 79 mmol) for 4 hrs under nitrogen. After the solvent was removed by evaporation, the residue was redissolved in 100 mL of EtOAc, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, and stripped of all solvent to give 5.6 g of the white powder, 2,2,4-trimethylcyclopentanone oxime. FAB/MS: (MH^+)=142.

Example 37 B) The product of Example 37 A was dissolved in 50 mL of acetone and 50 mL of 1 N sodium hydroxide at 0 °C. Benzenesulfonyl chloride (7.8 g, 44 mmol) was added over 5 min. The reaction mixture was allowed to warm up and stirred for 18 hrs until complete as determined by shift in HPLC retention time (Vydac C-18, linear gradient 5 % to 75 % acetonitrile/0.05 % TFA in water/0.05 % TFA over 20 min). The solvent was removed by evaporation and the residue redissolved in 100 mL EtOAc, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and stripped of all solvent by evaporation. The crude semisolid material was purified on Waters Deltapak C-

18 using a linear gradient from 10 % to 15 % acetonitrile(0.05 % TFA) in water (0.05 % TFA) over 20 min. The lyophilized product, 4,6,6-trimethylpiperidin-2-one, was a tan semisolid, 0.47 g. FAB/MS: (MH^+)=142.

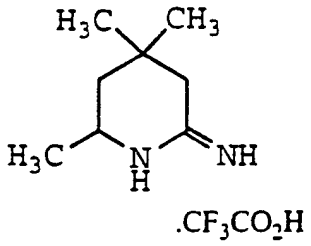
Example 37 C) To the product of Example 37 B (3.3 mmol) in 10 mL CH_2Cl_2 was added trimethyloxonium tetrafluoroborate (0.6 g, 4.0 mmol). After stirring 18 hrs, the reaction mixture was diluted with an additional 10 mL of CH_2Cl_2, washed with a saturated aqueous potassium carbonate solution, dried over magnesium sulfate, and stripped of all solvent to generate 2,3,4,5-tetrahydro-6-methoxy-2,2,4-trimethylpyridine.

Example 35) The product of Example 37 C was dissolved in 25 mL of methanol and refluxed with ammonium chloride for 3 hrs. The solvent was removed by evaporation and the residue oil was dissolved in 25 mL of EtOAc, washed with water, and stripped of all solvent under reduced pressure to produce the crude product. The material was purified on Waters Deltapak C-18 using a linear gradient of 5% to 70% acetonitrile(0.05 % TFA) in water (0.05 % TFA) over 30 min. and lyophilized to give 0.075 g white powder title material. FAB/MS: (MH^+)=141.

^1H NMR ($CDCl_3$): δ 10.4 (bs, 1H); 9.7 (bs, 1H); 7.5 (bs, 1H); 2.6 (q, 1H); 2.0 (q, 2H); 1.8 (d, 2H); 1.4 (s, 3H); 1.3 (s, 3H); 1.1 (d, 3H).

Example 38

4,4,6-trimethylpiperidin-2-imine, trifluoroacetate salt



Example 38 A) A solution of 2,4,4-trimethylcyclopentanone (5.5 g, 44 mmol) in 35 mL ethyl acetate/25 mL water was refluxed with hydroxylamine hydrochloride (4.6 g, 66 mmol) and sodium acetate

trihydrate (10.8 g, 79 mmol) for 4 hrs under nitrogen. Removed solvent by evaporation, redissolved in 100 mL ethyl acetate and washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and then removed solvent to give 6.2 g of 2,4,4-trimethylcyclopentanone oxime as a white powder. FAB/MS: $(MH^+)=142$.

Example 38 B) The product of Example 38 A was dissolved in 50 mL acetone and 50 mL 1 N sodium hydroxide at 0 °C. Benzenesulfonyl chloride was then added (7.8 g, 44 mmol) over 5 min. The reaction mixture was allowed to warm up and stir for 18 hrs until complete, as determined by the shift in HPLC retention time (Vydac C-18, linear gradient 5 % to 75 % acetonitrile/0.05 % TFA in water/0.05 % TFA over 20 min). The solvent was removed by evaporation and the residue was redissolved in 100 mL EtOAc, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and stripped of all solvent by evaporation. The semisolid product was purified on a Waters Deltapak C-18 using a linear gradient from 10% to 15% acetonitrile(0.05 % TFA) in water (0.05 % TFA) over 20 min. The lyophilized product, 6,4,4-trimethylpiperidin-2-one, was a tan semisolid, 0.75 g. FAB/MS: $(MH^+)=142$.

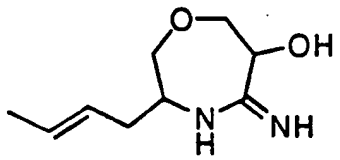
Example 38 C) To the product of Example 38 B (5.3 mmol) in 15 mL CH_2Cl_2 was added trimethyloxonium tetrafluoroborate (0.9 g, 6.0 mmol). After stirring 18 hrs, the reaction mixture was diluted with an additional 15 mL of CH_2Cl_2, washed with saturated aqueous potassium carbonate solution, dried over magnesium sulfate, and stripped of all solvent to give 0.69 g of 2,3,4,5-tetrahydro-6-methoxy-2,4,4-trimethylpyridine as an oil.

Example 38) The product of Example 38 C was dissolved in 25 mL of methanol and refluxed with ammonium chloride (0.25 g, 4.6 mmol) for 3 hrs. The solvent was removed by evaporation and the residue oil was dissolved in 25 mL EtOAc, washed with water, and stripped of all solvent. The residue was purified on a Waters Deltapak C-18 using a linear gradient of 5% to 70% acetonitrile (0.05 % TFA) in water (0.05 % TFA) over 30 min. and lyophilized to give 0.66 g of the title material as a white powder. FAB/MS: $(MH^+)=141$.

^{1}H NMR ($CDCl_3$): δ 10.4 (bs, 1H); 9.5 (bs, 1H); 8.1 (bs, 1H); 3.8 (m, 1H); 2.3 (q, 2H); 1.75 (d, 2H); 1.3 (d, 3H); 1.1 (s, 3H); 1.0 (s, 3H).

Example 39

3-(2-butenyl)hexahydro-5-imine-1,4-oxazepin-6-ol, trifluoroacetate salt



.TFA

Isomer A

Example 39 A) A sample of the 3-(2-Buten-1-yl)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 17 (6.6 g, 39 mmol), di-t-butyl dicarbonate (17.5 g, 80 mmol) and 4-dimethylaminopyridine (200 mg) were refluxed in anhydrous THF (80 mL) overnight. The contents were allowed to cool, diluted with EtOAc, and washed with 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo leaving an oil (12.9 g). The oil was purified by chromatography on silica gel eluting with 10% EtOAc/hexanes to give 4-N-Boc-3-(2-buten-1-yl)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine as a colorless oil (3.7 g).

Example 39 B) To the 4-N-Boc-3-(2-buten-1-yl)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 39 A (3.1 g, 12 mmol) in anhydrous THF (60 mL) at -78 °C was added dropwise lithium bis(trimethylsilyl)amide (1M in THF, 12 mL) keeping the temperature below -70 °C. The contents were allowed to warm to -40 °C and then cooled back to -78 °C. A solution of (1S)-(+)-(10-camphorsulfonyl)oxaziridine (3.0 g, 13 mmol) in THF (30 mL) was added dropwise. The contents were warmed to -25 °C and stirred 3 hours before pouring into saturated NH_4Cl and extracting with EtOAc. The EtOAc layer was dried over $MgSO_4$ and concentrated in vacuo to provide 4-N-Boc-3-(2-buten-1-yl)-6-

hydroxy-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine as a waxy solid.

Example 39 C) The 4-N-Boc-3-(2-buten-1-yl)-6-hydroxy-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 39 B (600 mg), t-butyldimethylsilyl chloride (2.0 g), imidazole (1.6 g) and anhydrous THF (50 mL) were stirred overnight. The contents were partitioned between EtOAc and water. The EtOAc layer was dried over $MgSO_4$ and concentrated in vacuo to generate an oil. This oil was chromatographed on silica gel eluting with 25% EtOAc/hexanes to give 4-N-Boc-3-(2-buten-1-yl)-6-(t-butyldimethylsilyloxy)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine as an oil (400 mg).

Example 39 D) The 4-N-Boc-3-(2-Buten-1-yl)-6-(t-butyldimethylsilyloxy)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 39 C (400 mg, 1 mmol) and magnesium perchlorate (45 mg) were heated at 50 °C in CH_3CN (25 mL) for 3 hours. The contents were allowed to cool and were partitioned between EtOAc and water. The EtOAc layer was dried over $MgSO_4$ and concentrated in vacuo leaving 3-(2-Buten-1-yl)-6-(t-butyldimethyl-silyloxy)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine as an oil (300 mg).

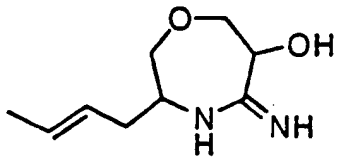
Example 39) The 3-(2-Buten-1-yl)-6-(t-butyldimethylsilyloxy)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 39 D (300 mg, 1 mmol) and $Me_3O^+BF_4^-$ (150 mg, 1 mmol) were stirred in CH_2Cl_2 overnight. The contents were concentrated in vacuo, the residue dissolved in methanol, and anhydrous ammonia bubbled into the solution. The reaction was stoppered and stirred overnight. The contents were concentrated in vacuo leaving a yellow oil (366 mg). The oil was purified by C-18 reverse phase chromatography eluting with a CH_3CN/H_2O to give the title products of this Example 39 (isomer A , 16 mg) and Example 40 (isomer B, 11 mg) as oils.

Mass spectral analysis for $C_9H_{16}N_2O_2$: M^+H = 185.

^1H NMR (D_2O): δ 5.60 - 5.42 (m, 1H); 5.35 - 5.20 (m, 1H); 4.75 - 4.60 (m, 1H); 3.95 - 3.50 (m, 5H); 2.35 - 2.20 (m, 2H); 1.60 - 1.45 (m, 3H)

Example 40

3-(2-butenyl)hexahydro-5-imine-1,4-oxazepin-6-ol, trifluoroacetate salt



.TFA

Isomer B

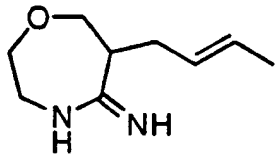
The crude product oil of Example 39 was purified by C-18 reverse phase chromatography eluting with a CH_3CN/H_2O to give the title products of Example 39 and title product of Example 40 (isomer B, 11 mg).

Mass spectral analysis for $C_9H_{16}N_2O_2$: M^+H = 185

^1H NMR (D_2O): δ 5.65 - 5.45 (m, 1H); 5.35 - 5.20 (m, 1H); 4.90 - 4.75 (m, 1H); 3.90 - 3.45 (m, 4H); 3.35 - 3.20 (m, 1H); 2.25 - 2.05 (m, 2H); 1.60 - 1.45 (m, 3H).

Example 41

6-(2-butenyl)hexahydro-1,4-oxazepin-5-imine, trifluoroacetate salt



.TFA

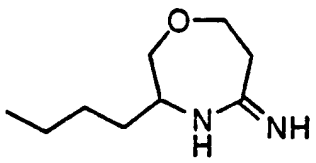
The title material was prepared according to the procedure of Example 18, using the 6-(2-Butenyl)tetrahydro-1,4-oxazepin-5(2H)-one isolated in Example 17.

Mass spectral analysis for $C_9H_{16}N_2O$: M^+H = 169.

^1H NMR (D_2O): δ 5.65 - 5.50 (m, 1H); 5.40 - 5.20 (m, 1H); 3.95 - 3.25 (m, 6H); 2.80 - 2.60 (m, 1H); 2.50 - 2.30 (m, 2H); 1.60 - 1.50 (m, 3H).

Example 42

3-butylhexahydro-1,4-oxazepin-5-imine, trifluoroacetate salt



.TFA

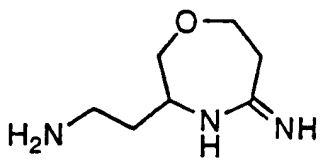
The product of Example 18 (1.3 g, 4.6 mmole), 5% rhodium/carbon (400 mg), ethanol (30 mL) and glacial acetic acid (30 mL) were shaken on a Parr hydrogenator at 55 psi of hydrogen overnight. The reaction contents were filtered and the filtrate was concentrated in vacuo leaving an oil (1.1 g). The oil was purified by C-18 reverse phase chromatography eluting with a CH_3CN/H_2O to give the title product as an oil (701 mg, 54% yield).

Mass spectral analysis for $C_9H_{18}N_2O$: M^+H = 171.

^1H NMR ($CDCl_3$): δ 9.90 (s, 1H); 9.50 (s, 1H); 8.90 (s, 1H); 4.00 - 3.40 (m, 6H); 3.00 - 2.70 (m, 2H); 1.80 - 1.20 (m, 6H); 1.00 - 0.80 (m, 3H).

Example 43

hexahydro-5-imino-1,4-oxazepine-3-ethanamine, bis(trifluoroacetate) salt



.2TFA

Example 43 A) To 2-nitroethanol (Aldrich, 50 mL, 0.7 mol) in CH_2Cl_2 (50 mL) was added dropwise acetyl chloride (53.3 mL, 0.75 mol) in CH_2Cl_2 (50 mL). The contents were stirred overnight,

washed with water, dried over $MgSO_4$ and concentrated in vacuo leaving 1-acetyl-2-nitroethanol as a light yellow oil (86 g).

Example 43 B) A sample of tetrahydropyran-4-one (Aldrich, 30 g, 0.3 mol) and morpholine (Aldrich, 30.5 mL, 0.35 mol) were refluxed in benzene (500 mL) for 3 hr with a Dean Stark trap to collect the water. The contents were allowed to cool and were concentrated in vacuo. The residue was dissolved in acetonitrile (250 mL) and added dropwise to a solution of the 1-acetyl-2-nitroethanol product of Example 48 A (46.6 g, 0.35 mol) in acetonitrile (250 mL) at -20 °C. The reaction contents were stirred overnight coming to room temperature and concentrated in vacuo. The residue was partitioned between Et_2O and water. The ether layer was dried over $MgSO_4$ and concentrated in vacuo leaving an oil. The oil was distilled on a Kugelrohr apparatus at 100 °C (0.1 mm) to give 2-nitroethyltrahydropyran-4-one as an oil which partially solidified (20.9 g).

Example 43 C) The 2-Nitroethyltetrahydropyran-4-one product of Example 43 B, hydroxylamine-O-sulfonic acid, and formic acid (98%) are refluxed for 0.5 hr. The contents are allowed to cool and concentrated in vacuo. The residue is partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer is dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by C-18 reverse phase chromatography to give 3-(2-nitroethyl)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine.

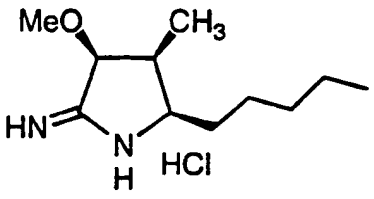
Example 43 D) To the 3-(2-nitroethyl)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 43 C in CH_2Cl_2 (25 mL) is added $Me_3O^+BF_4^-$ and the contents are stirred overnight. After concentrating in vacuo, the residue is dissolved in methanol (25 mL) and anhydrous ammonia is bubbled through the solution. Contents are stoppered and stirred 72 hours. Contents are concentrated in vacuo and the residue is purified by C-18 reverse phase chromatography eluting with a CH_3CN/H_2O gradient (0.05% TFA) to give 3-(2-nitroethyl)-5-imino-2,3,4,5,6,7-hexahydro-1,4-oxazepine.

Example 43) A sample of the 3-(2-Nitroethyl)-5-imino-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 43 C and palladium black in ethanol are shaken at 55 psi hydrogen on a Parr hydrogenation apparatus overnight. The contents are filtered and the filtrate is concentrated in vacuo. The residue

is purified by C-18 reverse phase chromatography to give the title compound.

Example 44

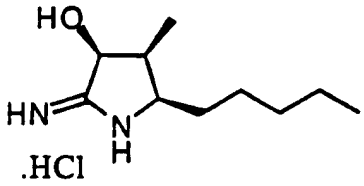
(±) 3α-methoxy-4α-methyl-5α-pentylpyrrolidin-2-imine, monohydrochloride



Example 44 was prepared from Example 45e, iodomethane, and sodium hydride. The synthesis of Example 44 is completed in the manner described in Example 45.

Example 45

(±) 2-imino-4α-methyl-5α-pentyl-3α-pyrrolidinol, monohydrochloride



Example 45A) To a stirring solution of methyl crotonate (3.28 g, 32.8 mmol) and nitromethane (1.08 g, 16.0 mmol) in 20 mL of CH_3CN was added DBU (2.39 mL, 16.0 mL). After 72 h, the reaction was concentrated under reduced pressure. The residue was taken up in EtOAc. The EtOAc solution was washed with 0.5 N HCl and brine, was dried over Na_2SO_4 anhydrous, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to give 3.05 g.

Example 45B,C) Example 45A (34 g, 0.15 mol) was reduced under catalytic hydrogenation conditions using Raney Ni in MeOH. After heating the reaction mixture for 16 h at 55 °C, the solvent was removed under vacuum. The crude lactam was separated by column chromatography into the cis (45B) and trans (45C) lactam.

Example 45D) A stirring solution of Example 45B (20 g, 0.12 mol), $(BocO)_2O$ (38.7 g, 0.18 mol), DMAP (14.4 g, 0.12 mol) in 500 mL of THF was heated at reflux for 3 h. After concentrating reaction under vacuum, the residue was taken up in EtOAc and washed with $KHSO_4$ and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and stripped. The crude product was purified by column chromatography to yield 31 g.

Example 45E) To a stirring solution of Example 45D (2.7 g, 9.9 mmol) and HMPA (1.8 g, 10.0 mmol) in 15 mL of THF cooled to -70 °C was added lithium hexamethyldisilazide (1.7 g, 10.0 mmol). After 20 min, the reaction was warmed to -40 °C and cooled again to -70 °C. To the stirring reaction was added (R)-(-)-(camphorsulphonyl)oxaziridine (2.4 g, 10.4 mmol) in 7 mL of THF. After stirring at -70 °C for 30 min, the reaction was warmed to -30 °C and stirred an additional 2.5 h. To the reaction was added saturated NH_4Cl solution followed by EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and stripped. The crude product was purified by column chromatography to yield 1.3 g of 3-hydroxylactam.

Example 45F) To a solution of Example 45E (1.3 g) in CH_2Cl_2 was added TFA (6 mL). After 2 h, the reaction was concntrated under vacuum to give 0.85 g of product.

Example 45G) To a stirring solution of Example 45F (0.85 g, 4.6 mmol) and imidazole (0.35 g, 4.6 mmol) in 15 mL was added t-butyldimethylsilylchloride (0.70 g, 4.6 mmol). After 18 h, the reaction mixture was concentrated under high vacuum. To the residue was added EtOAc. The organic layer was washed with $KHCO_3$ solution, H_2O, and brine, dried over anhydrous Na_2SO_4, filtered, and stripped to yield 1.1 g of product.

Example 45H) A solution of Example 45G (1.1 g, 3.7 mmol) and trimethyloxonium tetrafluoroborate (0.6 g, 4.7 mmol) in 30 mL

was stirred for 72 h at ambient temperature. After removing solvent under vacuum, the residue was dissolved in EtOAc. The organic layer was washed with $KHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and stripped to yield 1 g of product.''

Example 45I) Example 45H (1 g) in MeOH was treated with NH_4Cl (0.3 g) under 12 Kbar of pressure. The reaction was concentrated under vacuum. The residue was taken up in CH_2Cl_2, filtered, and stripped to give 0.8 g of product.

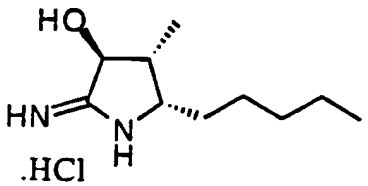
Example 45) To a solution of Example 45I (0.8 g) in 40 mL of MeOH was added 10 mL of 1 N HCl. After 1.5 h, the reaction mixture was concentrated under vacuum. The residue was partitioned between 0.05 N HCl and CH_2Cl_2. The aqueous layer stripped. The residue was purified by chromatography on a reverse phase C-18 column to give two alcohols. The first eluting was Example 46 and the second eluting was Example 45.

Elemental analysis: $C_{10}H_{20}N_2O \cdot 1\ HCl \cdot 0.2\ H_2O$ (MW=224.35)

	C	H	N	Cl
Calculated:	53.80	9.61	12.49	15.80
Found:	53.80	9.47	12.14	15.46

Example 46

(±) 2-imino-4α-methyl-5α-pentyl-3β-pyrrolidinol, monohydrochloride



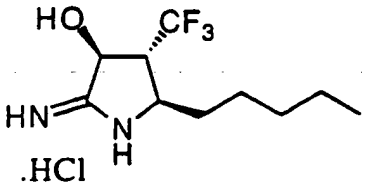
The synthesis and isolation of Example 46 was described in Example 45.

Elemental analysis: $C_{10}H_{20}N_2O \cdot 1\ HCl \cdot 0.2\ H_2O$ (MW=224.35)

	C	H	N	Cl
Calculated:	53.80	9.61	12.49	15.80
Found:	53.78	9.37	12.14	15.78

Example 47

(±) 2-imino-5α-pentyl-4β-(trifluoromethyl)-3α-pyrrolidinol, monohydrochloride



Example 47A) A suspension of ethyl 4,4,4-trifluorocrotonate (10.0 g, 59 mmol), 1-nitrohexane (7.86 g, 60 mmol), K_2CO_3 (4.1 g), and Aliquot 336 (6 drops) was sonicated for 5 h. To the reaction was added Et_2O (200 mL). The reaction mixture was filtered, extracted with brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated under reduced pressure to give a yellow liquid. The product was purified by column chromatography to give 13.8 g (77%).

Example 47B,C) A solution of Example 47A (13.0 g) in MeOH was reduced under catalytic hydrogenation conditions (60 psi, 55 °C) using Raney nickel. The reaction was heated for 8 h to effect cyclization after reduction of the nitro group. After concentration of the reaction mixture under reduced pressure, the residue was purified by column chromatography to give 9.0 g of a light yellow liquid. A second column was run to separate the cis (47B) and trans lactam (47C).

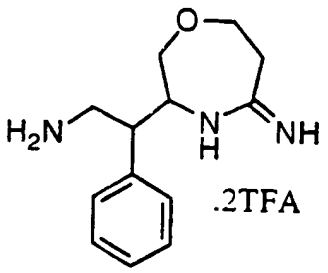
Example 47D) Example 47C was treated in the manner described in Example 45D and following to prepare Example 47.

Elemental analysis: $C_{10}H_{17}N_2F_3O \cdot 1\ HCl$ (MW=274.71)

	C	H	N	Cl
Calculated:	43.72	6.60	10.20	12.91
Found:	43.62	6.44	10.15	12.73

Example 48

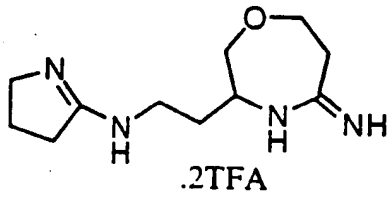
hexahydro-5-imino-β-phenyl-1,4-oxazepine-3-ethanamine, bis(trifluoroacetate) salt



The title product is prepared according to the procedure of Example 43, using β-nitrostyrene instead of 1-acetyl-2-nitroethanol to afford the title product.

Example 49

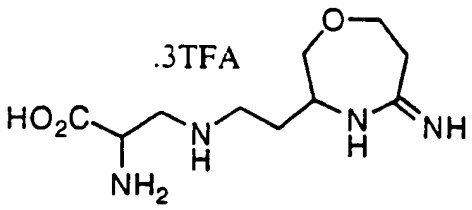
N-(3,4-dihydro-2H-pyrrol-5-yl)hexahydro-5-imino-1,4-oxazepine-3-ethanamine, bis(trifluoroacetate) salt



Example 43 is allowed to react with 2-methoxypyrroline to afford the title product.

Example 50

3-[[2-(hexahydro-5-imino-1,4-oxazepin-3-yl)ethyl]amino]alanine, tris(trifluoroacetate) salt

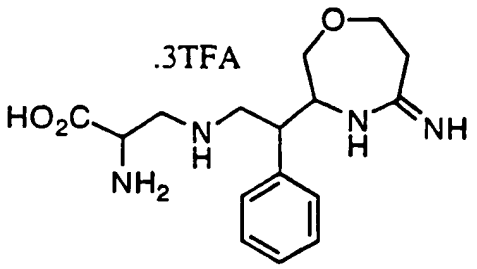


Example 50 A) Example 43 is allowed to react with N-CBZ-dehydroalanine methyl ester to afford the protected title product.

Example 50) Removal of the CBZ protecting group from Example 50 A by hydrogenation followed by acid hydrolysis affords the title product.

Example 51

3-[[2-(hexahydro-5-imino-1,4-oxazepin-3-yl)-2-phenylethyl]amino]alanine, tris(trifluoroacetate) salt

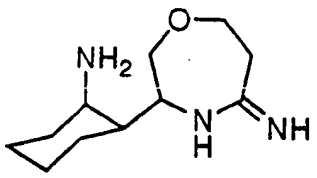


Example 51 A) Example 48 is allowed to react with N-CBZ-dehydroalanine methyl ester to afford the protected title product.

Example 51) Removal of the CBZ protecting group from example 51a by hydrogenation followed by acid hydrolysis affords the title product.

Example 52

2-(hexahydro-5-imino-1,4-oxazepin-3-yl)cyclohexanamine, bis(trifluoroacetate) salt



.2TFA

The title product is prepared by the method of Example 43 using 2-nitrocyclohexanol in place of 2-nitroethanol.

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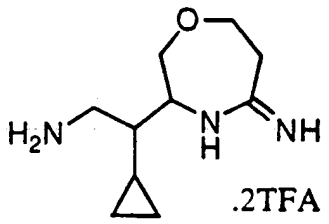
Example 53

β-cyclopropylhexahydro-5-imino-1,4-oxazepine-3-ethanamine, bis(trifluoroacetate) salt

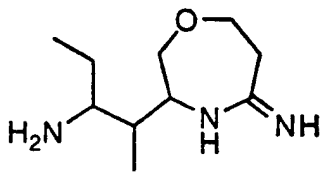


Example 53 A) 2-nitro-2-cyclopropylethanol is prepared from cyclopropylcarboxaldehyde via the Henry reaction.

Example 53) The title product is prepared by the method of Example 43 using the 2-nitro-2-cyclopropylethanol product of Example 53 A in place of 2-nitroethanol.

Example 54

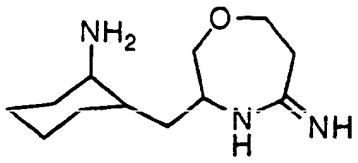
α-ethylhexahydro-5-imino-β-methyl-1,4-oxazepine-3-ethanamine, bis(trifluoroacetate) salt



The title product is prepared by the method of Example 43 using 3-nitro-4-hydroxypentane in place of 2-nitroethanol.

Example 55

2-(hexahydro-5-imino-1,4-oxazepin-3-yl)cyclohexanamine, bis(trifluoroacetate) salt



.2TFA

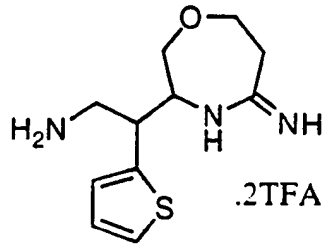
Example 55 A) Tetrahydropyran-4-one is allowed to react with o-nitrobenzyl bromide under basic conditions to give 2-(o-nitrobenzyl)tetrahydropyran-4-one.

Example 55 B) The 2-(o-nitrobenzyl)tetrahydropyran-4-one product of Example 55 A is carried on as in Example 43c-d to give 3-(o-nitrobenzyl)-5-imino-2,3,4,5,6,7-hexahydro-1,4-oxazepine.

Example 55) The 3-(o-nitrobenzyl)-5-imino-2,3,4,5,6,7-hexahydro-1,4-oxazepine product of Example 55 A is reduced under hydrogen atmosphere utilizing platinum oxide catalyst to afford the title product.

Example 56

hexahydro-5-imino-β-(2-thienyl)-1,4-oxazepine-3-ethanamine, bis(trifluoroacetate) salt

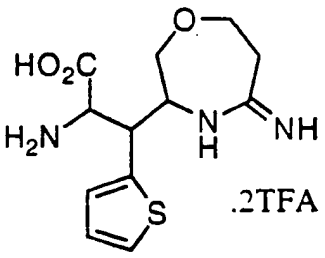


.2TFA

The title material is prepared according to the procedure of Example 48 using 1-nitro-2-(2-thiophenyl)ethene.

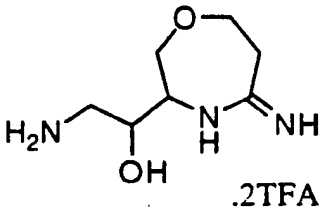
Example 57

α-aminohexahydro-5-imino-β-(2-thienyl)-1,4-oxazepine-3-propanoic acid, bis(trifluoroacetate) salt



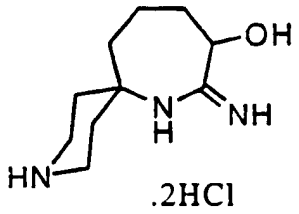
Example 58

α-(aminomethyl)hexahydro-5-imino-1,4-oxazepine-3-methanol, bis(trifluoroacetate) salt



Example 59

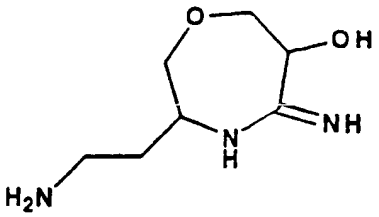
8-imino-3,7-diazaspiro[5.6]dodecan-9-ol, dihydrochloride



7-(Spiro-4-piperidinyl-N-Z)caprolactam is treated as described in Example 34 to give the title compound.

Example 60

3-(2-aminoethyl)hexahydro-5-imino-1,4-oxazepin-6-ol, bis(trifluoroacetate) salt

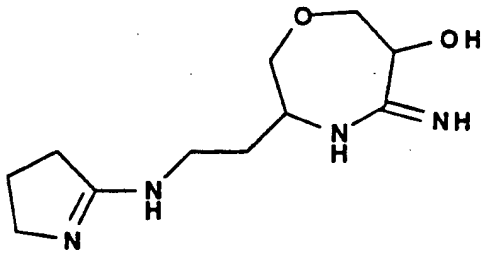


Example 60 A) The product of Example 43C is reacted as in Example 39 to afford 3-(2-nitroethyl)hexahydro-5-imino-1,4-oxazepin-6-ol.

Example 60) 3-(2-nitroethyl)hexahydro-5-imino-1,4-oxazepin-6-ol is reduced as in Example 43 to afford the title compound.

Example 61

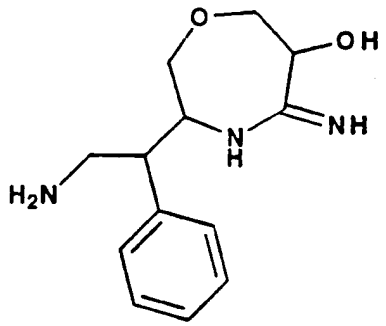
hexahydro-5-imino-3-[2-[(2-pyrrolidinylidene)amino]ethyl]-1,4-oxazepin-6-ol, bis(trifluoroacetate) salt



The product of Example 60 is reacted as in Example 49 to afford the title compound.

Example 62

3-(2-amino-1-phenylethyl)hexahydro-5-imino-1,4-oxazepin-6-ol, bis(trifluoroacetate) salt



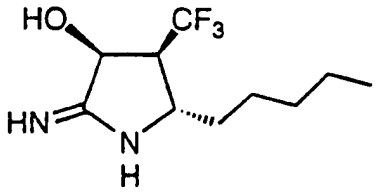
Example 62 A) 3-(2-Nitro-1-phenylethyl)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine is prepared as in Example 43, using β-nitrostyrene instead of 1-acetyl-2-nitroethanol.

Example 62 B) 3-(2-Nitro-1-phenylethyl)-5-oxo-2,3,4,5,6,7-hexahydro-1,4-oxazepine is reacted as in Example 39 to afford 3-(2-nitro-1-phenylethyl)-6-hydroxy-5-imino-2,3,4,5,6,7-hexahydro-1,4-oxazepine.

Example 62) 3-(2-Nitro-1-phenylethyl)-6-hydroxy-5-imino-2,3,4,5,6,7-hexahydro-1,4-oxazepine is reduced as in Example 43 to afford the title compound.

Example 63

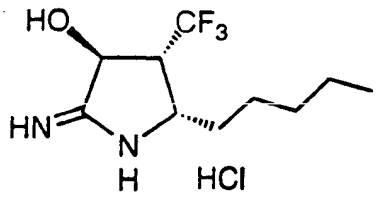
(±) 2-imino-4α-(trifluoromethyl)-5β-pentylpyrrolidin-3α-ol



Example 63 is synthesized and isolated from Example 47.

Example 64

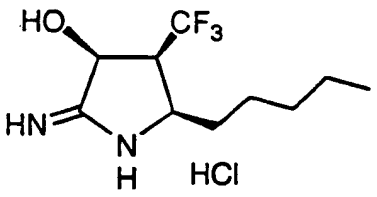
(±) 2-imino-4β-(trifluoromethyl)-5β-pentylpyrrolidin-3α-ol



Example 64 is prepared from Example 47B in the manner described in Example 47.

Example 65

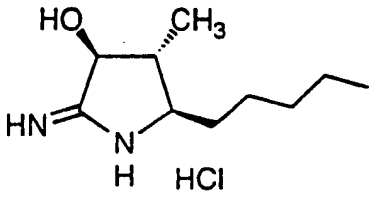
(±) 2-imino-4α-(trifluoromethyl)-5α-pentylpyrrolidin-3α-ol



Example 65 is prepared from Example 47B in the manner described in Example 47.

Example 66

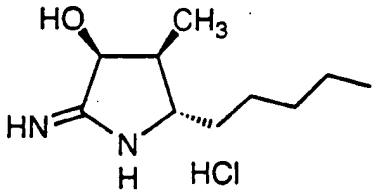
(±) 2-imino-4β-methyl-5α-pentylpyrrolidin-3α-ol



Example 66 is prepared from Example 45C in the manner described in Example 45.

Example 67

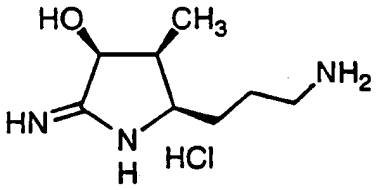
(±) 2-imino-4α-methyl-5β-pentylpyrrolidin-3α-ol



Example 67 is prepared from Example 45C in the manner described in Example 45.

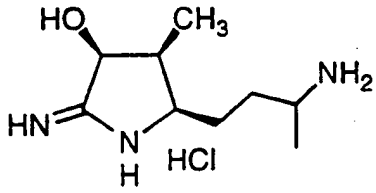
Example 68

(±) 5α-(3-aminopropyl)2-imino-4α-methylpyrrolidin-3α-ol, dihydrochloride



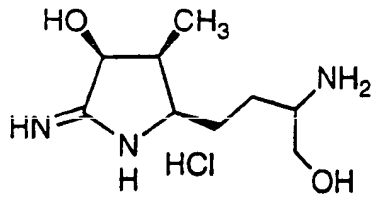
Example 69

(±) 5α-(3-aminobutyl)-2-imino-4α-methylpyrrolidin-3α-ol, dihydrochloride



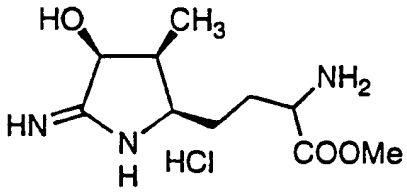
Example 70

(±) α-amino-4α-hydroxy-5-imino-3α-methylpyrrolidine-2α-butanol, dihydrochloride



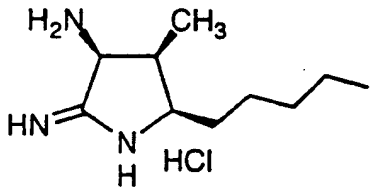
Example 71

(±) methyl α-amino-4α-hydroxy-5-imino-3α-methylpyrrolidine-2α-butanoate, dihydrochloride



Example 72

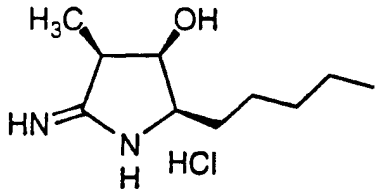
(±) 2-imino-4α-methyl-5α-pentylpyrrolidin-3α-amine, dihydrochloride



Example 72 is prepared from Example 45E and Boc_2NH by Mitsunobu reaction conditions. The synthesis of Example 72 is completed in the manner described in Example 45.

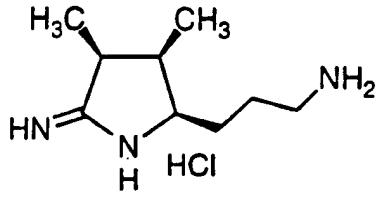
Example 73

(±) 5-imino-4α-methyl-2α-pentylpyrrolidin-3α-ol, monohydrochloride



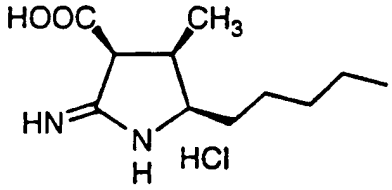
Example 74

(±) 5-imino-3α,4α-dimethylpyrrolidin-2α-propanamine, dihydrochloride



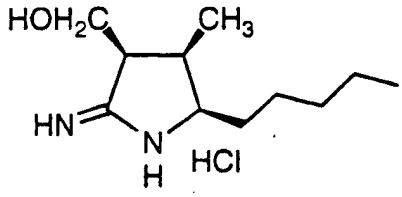
Example 75

(±) 2-imino-4α-methyl-5α-pentylpyrrolidine-3α-carboxylic acid, monohydrochloride



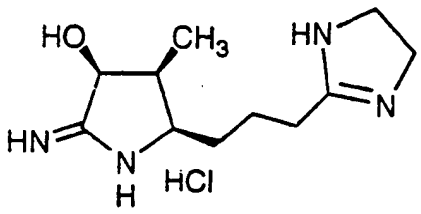
Example 76

(±) 2-imino-4α-methyl-5α-pentylpyrrolidine-3α-methanol, monohydrochloride



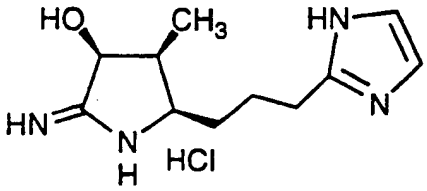
Example 77

(±) 5α-[3-(4,5-dihydro-1H-imidazol-2-yl)propyl]-2-imino-4α-methylpyrrolidin-3α-ol, dihydrochloride



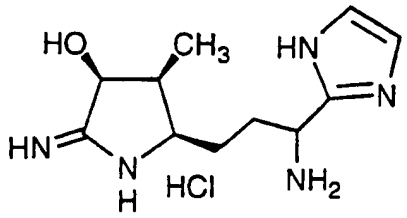
Example 78

(±) 5α-[3-(1H-imidazol-2-yl)propyl]-2-imino-4α-methylpyrrolidin-3α-ol, dihydrochloride



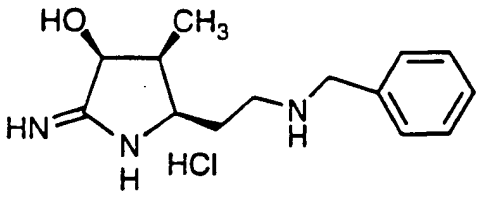
Example 79

(±) 5α-[3-amino-3-(1H-imidazol-2-yl)propyl]-2-imino-4α-methylpyrrolidin-3α-ol, trihydrochloride



Example 80

(±) 2-imino-4α-methyl-5α-[3-[(phenylmethyl)amino]propyl]pyrrolidin-3α-ol, dihydrochloride



Example 80 A) *cis* and *trans*-5-[(1,3-dioxolan-2-yl)methyl]-4-(methyl)pyrrolidin-2-one was prepared in the manner described in R. Ohrlein, W. Schwab, R. Ehrler, V. Jager, *Synthesis* **1986**, 535-538) starting with 1,1-dimethoxy-3-nitropropane and methyl crotonate.

Example 80 B,C) Example 80 A was reduced under catalytic hydrogenation conditions using Raney Ni in MeOH. After heating the reaction mixture for 16 h at 55 °C, the solvent was removed under vacuum. The crude lactam was separated by column chromatography into the cis (80 B) and trans (80C) lactam.

Example 80 D) A stirring solution of Example 80 B , $(BocO)_2O$, DMAP in THF is heated at reflux for 3 h. After concentrating reaction under vacuum, the residue is taken up in EtOAc and washed with $KHSO_4$ and brine. The organic layer is dried over anhydrous Na_2SO_4, filtered, and stripped. The crude product is purified by column chromatography.

Example 80 E) To a stirring solution of Example 80 D and HMPA in THF cooled to -70 °C is added lithium hexamethyldisilazide. After 20 min, the reaction is warmed to -40 °C and cooled again to -70 °C. To the stirring reaction is added (R)-(-)-(camphorsulphonyl)oxaziridine in THF. After stirring at -70 °C for 30 min, the reaction is warmed to -30 °C and stirred an additional 2.5 h. To the reaction is added saturated NH_4Cl solution followed by EtOAc. The organic layer is washed with brine, dried over anhydrous Na_2SO_4, filtered, and stripped. The crude product is purified by column chromatography to yield 1.3 g of 3-hydroxylactam.

Example 80 F) To a stirring solution of Example 80 E in $CHCl_3$ is added H_2O and TFA. After stirring for 2 h, the reaction mixture is concentrated under reduced pressure. The residue is dissolved in EtOAc. The organic layer is washed with a

minimum of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to recover crude aldehyde.

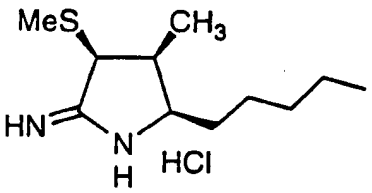
Example 80 G) To a sirring solution of Example 80 F in MeOH is added $NaBH_3CN$. The reaction is maintained at pH 4 by the addition of HOAc. After stirring for three days, the reaction mixture is concentrated under vacuum. To the residue is added 1 N HCl and EtOAc. After separating the layers, the aqueous phase is neutralized with $NaHCO_3$ and extracted with EtOAc. After concentrating the organic phase, the residue is treated with 1 N HCl and lyophilized. The resulting solid is purified by reverse phase column chromatography on a C-18 column.

Example 80 H) The product of Example 80 G is treated with trimethyloxonium tetrafluoroborate in CH_2Cl_2 as described in Example 45.

Example 80) A solution of the product of Example 80 H in MeOH is reacted with ammonium chloride by the method of Example 5 followed by chromatography on reverse phase HPLC to generate the title material.

Example 81

4α-methyl-5α-pentyl-3α-(methylthio)pyrrolidin-2-imine, monohydrochloride



Biological Data

The activity of the above listed compounds as NO synthase inhibitors has been determined in the following assays:

Citrulline Assay for Nitric Oxide Synthase

Nitric oxide synthase (NOS) activity was measured by monitoring the conversion of [3H]-arginine to [3H]-citrulline (Bredt and Snyder, Proc. Natl. Acad. Sci. U.S.A., 87, 682-685, 1990 and Misko et al, Eur. J. Pharm., 233, 119-125, 1993). Human inducible NOS (hiNOS), human endothelial constitutive NOS (hecNOS) and human neuronal constitutive NOS (hncNOS) were each cloned from RNA extracted from human tissue. The cDNA for human inducible NOS (hiNOS) was isolated from a λcDNA library made from RNA extracted from a colon sample from a patient with ulcerative colitis. The cDNA for human endothelial constitutive NOS (hecNOS) was isolated from a λcDNA library made from RNA extracted from human umbilical vein endothelial cells (HUVEC) and the cDNA for human neuronal constitutive NOS (hncNOS) was isolated from a λcDNA library made from RNA extracted from human cerebellum obtained from a cadaver. The recombinant enzymes were expressed in Sf9 insect cells using a baculovirus vector (Rodi et al, in The Biology of Nitric Oxide, Pt. 4: Enzymology, Biochemistry and Immunology; Moncada, S., Feelisch, M., Busse, R., Higgs, E., Eds.; Portland Press Ltd.: London, 1995; pp 447-450). Enzyme activity was isolated from soluble cell extracts and partially purified by DEAE-Sepharose chromatography. To measure NOS activity, 10 µL of enzyme was added to 40 µL of 50 mM Tris (pH 7.6) in the presence or absence of test compounds and the reaction initiated by the addition of 50 µL of a reaction mixture containing 50 mM Tris (pH 7.6), 2.0 mg/mL bovine serum albumin, 2.0 mM DTT, 4.0 mM $CaCl_2$, 20 µM FAD, 100 µM tetrahydrobiopterin, 0.4-2.0 mM NADPH and 60 µM L-arginine containing 0.9 µCi of L-[2,3-^{3}H]-arginine. The final concentration of L-arginine in the assay was 30 µM. For hecNOS, and hncNOS, calmodulin was included at a final concentration of 40-100 nM. Following incubation at 37° C for 15 minutes, the reaction was terminated by addition of 300 µL of cold stop buffer containing 10 mM EGTA, 100 mM HEPES, pH 5.5 and 1 mM citrulline. [3H]-Citrulline was separated by chromatography on Dowex 50W X-8 cation exchange resin and radioactivity determined with a liquid scintillation counter. Results are reported in Table I as the IC_{50} values of compounds for hiNOS, hecNOS and hncNOS. Compounds giving less than 50% inhibition at 100 µM were reported as having IC_{50} values of >100 µM and compounds

giving greater than 50% inhibition at 100 μM were reported as having IC_{50} values of <100 μM.

The following Examples were assayed with the following results.

Table I

Example	IC_{50} [μM] hiNOS	hecNOS	hncNOS
10	>100		
13	<100	<100	<100
18	<100	>100	>100
21	>100	>100	>100
36	>100		
37	<100	<100	<100
38	>100	<100	<100
39	<100	>100	<100
40	<100	>100	<100
41	>100	>100	>100
42	<100	>100	<100
44	>100	>100	>100
45	<100	>100	<100
46	<100	>100	<100
47	<100	>100	<100

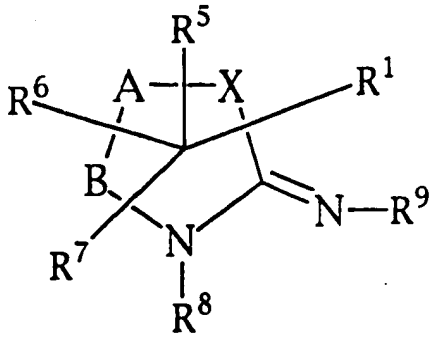
hiNOS refers to human inducible NOS

hecNOS refers to human endothelial constitutive NOS
hncNOS refers to human neuronal constitutive NOS

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed:

1. A compound having the formula:



and salts, and pharmaceutically acceptable esters thereof, wherein:

R^1 is selected from hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, alkyloxy, thioalkoxy, cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocyclyl, aryl, hydroxy, lower alkoxy, aryloxy, halogen, thiol, lower thioalkoxy, halogen, cyano, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl, alkylaminoaryl, acylamino, carboxy, carboxyalkyl, $CONR^{10}R^{11}$, $S(O)R^{10}$, $S(O)_2R^{10}$, $SO_2NR^{10}R^{11}$, $PO(OR^{10})(OR^{11})$, amidino, guanidino;

wherein all said substitutions may be optionally substituted with one or more of the following: halogen, lower alkyl, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, $S(O)R^{10}$, $S(O)_2R^{10}$, amidino, guanidino;

X = NR^2, O, S, SO, SO_2, $(CH_2)p$, CH=CH;

p = 0 to 6;

A = NR^3, O, S, SO, SO_2, $(CH_2)q$, CH=CH;

q = 0 to 6;

B = NR^4, O, S, SO, SO_2, $(CH_2)v$, CH=CH;

v = 0 to 6;

R^2 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^3 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^4 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^5, R^6, R^7 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, $S(O)R^9$, $S(O)_2R^9$, halogen, nitro, amino, alkylamino, dialkylamino, aminoalkyl, dialkylaminoalkyl, arylamino, aminoaryl, alkylaminoaryl, acylamino, carboxyl, carboalkoxy, carboaryloxy, carboarylalkyloxy, cyano, aminocarbonylalkoxy, aminocarbonylamino, aminocarbonylaminoalkyl, haloalkyl, $SO_2NR^{10}R^{11}$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, halogen, amino, alkylamino, dialkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy;
R^5, R^6, may optionally be taken together to form an alicyclic hydrocarbon, heterocyclyl or aromatic hydrocarbon and said optionally formed ring may be optionally substituted with one or more of the following:
lower alkyl, lower alkenyl, lower alkynyl which may be optionally substituted with carboxyl, carboalkoxy, carboaryloxy, carboxyalkylaryloxy and lower alkoxy;

R^8 = hydrogen, hydroxy, alkyloxy;
R^9 = hydrogen, hydroxy, alkyloxy;
R^{10} = hydrogen, lower alkyl, alkylaryl, aryl;
R^{11} = hydrogen, lower alkyl, alkylaryl, aryl;
R^{10} and R^{11}, taken together, may be alkylene, resulting in a N-containing heterocycle;

With the proviso that when R^1 is lower alkyl, lower alkenyl, or lower alkynyl, R^1 cannot be optionally substituted by cycloalkyl, heterocyclyl, and aryl, unless one A, or B is NR^2, O, S, SO, SO_2;

With the proviso that when A and B are $(CH_2)_p$ or CH=CH, and R^1 is lower alkyl, lower alkenyl, or lower alkynyl R^1 is not

substituted by cycloalkyl, heterocyclyl, or aryl and R^5 and R^6 are not H;

With the proviso that only one of X, A, and B, may be selected from NR^2, NR^3, or NR^4, respectively, O, S, SO, or SO_2;

With the further proviso that when X=$(CH_2)p$; A=$(CH_2)q$, B=$(CH_2)v$, p+q+v=3, then no more than one of R^1, R^5, R^6 and R^7 can be alkyl, alkoxy, cycloalkyl or cycloalkoxy at the 5-position;

With one further proviso that when X=$(CH_2)p$; A=$(CH_2)q$, B=$(CH_2)v$, p+q+v=3, and one of R^1, R^5, R^6 and R^7 is an alkyl, cycloalkyl or aryl group at the 5-position, then none of the remaining R^1, R^5, R^6 and R^7 can be a cyano, substituted amino, alkoxy or thioalkoxy at the 5-position;

With the further proviso that when X=CH=CH, A=$(CH_2)q$, B=$(CH_2)v$ and q+v=2, then none of R^1, R^5, R^6 and R^7 can be carboxy at the 6-position; and

With the further proviso that when X=NH, A=$(CH_2)q$, B=$(CH_2)v$ and q+v=4, then none of R^1, R^5, R^6 and R^7 can be carboxy at the 7-position.

2. The compound as recited in Claim 1 wherein:

R^1 is selected from hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkyloxy, thioalkoxy, cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocyclyl, aryl, hydroxy, lower alkoxy, aryloxy, halogen, thiol, lower thioalkoxy, amino, alkylamino, aminoalkyl, aminoaryl, carboxy, carboxyalkyl, $CONR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, amidino, guanidino; wherein all said substitutions may be optionally substituted with one or more of the following: halogen, lower alkyl, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy, amidino, guanidino;

X = NR^2, O, S, $(CH_2)p$, CH=CH;

p = 0 to 4;
A = NR^3, O, S, SO, SO_2, $(CH_2)q$, CH=CH;
q = 0 to 4;
B = NR^4, O, S, SO, SO_2, $(CH_2)v$, CH=CH;
v = 0 to 4;
R^2 = hydrogen, lower alkyl, aryl, heterocyclyl;
R^3 = hydrogen, lower alkyl, aryl, heterocyclyl;
R^4 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^5, R^6, R^7 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl, hydroxy, lower alkoxy, thiol, lower thioalkoxy, amino, alkylamino, aminoalkyl, arylamino, aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylalkoxy, aminocarbonylamino, aminocarbonylaminoalkyl, haloalkyl, $SO_2NR^{10}R^{11}$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, halogen, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, carboaryloxy, carboalkylaryloxy, hydroxy, lower alkoxy;

R^5, R^6, may optionally be taken together to form an alicyclic hydrocarbon, or heterocyclyl;

R^8 = hydrogen or hydroxy;
R^9 = hydrogen;
R^{10} = hydrogen or lower alkyl; and
R^{11} = hydrogen or lower alkyl.

3. The compound as recited in Claim 1 wherein:

R^1 is selected from hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, alkyloxy, thioalkoxy, cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by lower alkyl, lower alkenyl, lower alkynyl, halogen, cycloalkyl, heterocyclyl, aryl, hydroxy, lower alkoxy, aryloxy, amino, alkylamino, aminoalkyl, aminoaryl, carboxy, carboxyalkyl, $SO_2NR^{10}R^{11}$, amidino, guanidino; wherein all said substitutions may be optionally substituted with one or more of the following: halogen, lower alkyl, or amino,

alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, hydroxy, lower alkoxy, amidino, guanidino;

X = $(CH_2)p$, CH=CH;
p = 0 to 3;
A = NR^3, O, S, $(CH_2)q$, CH=CH;
q = 0 to 3;
B = NR^4, O, S, $(CH_2)v$, CH=CH;
v = 0 to 3;
R^3 = hydrogen, lower alkyl, aryl, heterocyclyl;
R^4 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^5, R^6, R^7 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl, hydroxy, lower alkoxy, amino, alkylamino, aminoalkyl, arylamino, aminoaryl, carboxyl, carboalkoxy, carboaryloxy, aminocarbonylamino, $SO_2NR^{10}R^{11}$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, halogen, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, hydroxy, lower alkoxy;

R^8 = hydrogen or hydroxy;
R^9 = hydrogen or hydroxy;
R^{10} = hydrogen or lower alkyl; and
R^{11} = hydrogen or lower alkyl.

4. The compound as recited in Claim 1 wherein:

R^1 is selected from hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, alkyloxy, thioalkoxy, cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocyclyl, aryl, hydroxy, lower alkoxy, aryloxy, amino, alkylamino, aminoalkyl, aminoaryl, carboxy, carboxyalkyl, $SO_2NR^{10}R^{11}$, amidino, guanidino;
wherein all said substitutions may be optionally substituted with one or more of the following: halogen, lower alkyl, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, hydroxy, lower alkoxy, amidino, guanidino;

X = $(CH_2)p$;
p = 0 to 3;
A = NR^3, oxygen, $(CH_2)q$, CH=CH;
q = 0 to 3;
B = O, $(CH_2)v$, CH=CH;
v = 0 to 3;
R^3 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^5, R^6, R^7 are independently selected from hydrogen, lower alkyl, lower alkenyl, lower alkynyl, heterocyclyl, hydroxy, lower alkoxy, amino, alkylamino, aminoalkyl, arylamino, aminoaryl, carboxyl, carboalkoxy, aminocarbonylamino, $SO_2NR^{10}R^{11}$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, hydroxy, lower alkoxy;
R^8 = hydrogen or hydroxy;
R^9 = hydrogen or hydroxy;
R^{10} = hydrogen or lower alkyl; and
R^{11} = hydrogen or lower alkyl.

5. The compound as recited in Claim 1 wherein:

R^1 is selected from hydrogen, hydroxy, lower alkyl, lower alkenyl, alkyloxy, thioalkoxy, cycloalkyl, heterocyclyl, and aryl, which may optionally be substituted by lower alkyl, lower alkenyl, halogen, aryl, hydroxy, lower alkoxy, aryloxy, amino, alkylamino, aminoalkyl, aminoaryl, carboxy, carboxyalkyl, $SO_2NR^{10}R^{11}$, amidino, guanidino.

X = $(CH_2)p$;
p = 0 to 3;
A = NR^3, oxygen, $(CH_2)q$, CH=CH;
q = 0 to 3;
B = $(CH_2)v$, CH=CH;
v = 0 to 3;
R^3 = hydrogen, lower alkyl, aryl, heterocyclyl;

R^5, R^6, R^7 are independently selected from hydrogen, lower alkyl, lower alkenyl, heterocyclyl, hydroxy, lower alkoxy, amino, alkylamino, aminoalkyl, arylamino, aminoaryl, carboxyl, carboalkoxy, aminocarbonylamino, $SO_2NR^{10}R^{11}$, wherein all said substitutions may be optionally substituted with one or more of the following: lower alkyl, halogen, amino, alkylamino, aminoalkyl, aminoacyl, carboxyl, carboalkoxy, hydroxy, lower alkoxy;

R^8 = hydrogen or hydroxy;

R^9 = hydrogen or hydroxy;

R^{10} = hydrogen or lower alkyl; and

R^{11} = hydrogen or lower alkyl.

6. The compound as defined in Claim 1 wherein the compound is selected from the group consisting of hexahydro-3,3,7-trimethyl-2H-azepin-2-imine, monohydrochloride; hexahydro-3,7,7-trimethyl-2H-azepin-2-imine, monohydrochloride; hexahydro-4,4,6,6-tetramethyl-2H-azepin-2-imine, monohydrochloride; tetrahydro-1,4-oxazepin-5(2H)-imine, trifluoroacetate salt; 3-(2-butenyl)tetrahydro-1,4-oxazepin-5(2H)-imine, trifluoroacetate salt; hexahydro-1-methyl-5H-1,4-diazepin-5-imine, trifluoroacetate salt; tetrahydro-3-(2-methoxyethyl)-1,4-oxazepin-5(2H)-imine, monohydrochloride; tetrahydro-6-(2-methoxyethyl)-1,4-oxazepin-5(2H)-imine, monohydrochloride; 4,4-dimethyl-5-pentylpyrrolidin-2-imine, monohydrochloride; 5-pentyl-4,4-bis(trifluoromethyl)pyrrolidin-2-imine, monohydrochloride; methyl 2-imino-4-methyl-5-pentylpyrrolidine-3-carboxylate, monohydrochloride; 2-imino-4-methyl-5-pentylpyrrolidine-3-carboxylic acid, monohydrochloride; α-amino-4-hydroxy-5-imino-3-(trifluoromethyl)pyrrolidine-2-butanoic acid, monohydrochloride; hexahydro-2-imino-4-methyl-7-(2-propenyl)-1H-azepin-3-ol; 6-butyl-3-hydroxy-4-methylpiperidin-2-imine, monohydrochloride; 6-imino-2,4-dimethylpiperidine-3-methanamine, dihydrochloride; 4,6,6-trimethylpiperidine-2-imine, trifluoroacetate salt; and 4,4,6-trimethylpiperidin-2-imine, trifluoroacetate salt.

7. A method of inhibiting nitric oxide synthesis in a subject in need of such inhibition by administering a therapeutically effective amount of a compound of claim 1,2,3,4,5 or 6.

8. A method of selectively inhibiting nitric oxide synthesis produced by inducible nitric oxide synthase over nitric oxide produced by the endothelial constitutive form of nitric oxide synthase in a subject in need of such inhibition by administering a therapeutically effective amount of a compound of claim 1,2,3,4,5 or 6.

9. A method of lowering nitric oxide levels in a subject in need of such by administering a therapeutically effective amount of a compound of claim 1,2,3,4,5 or 6.

10. A method of lowering nitric oxide levels in a subject in need of such by administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of claim 1,2,3,4,5, or 6 and together with at least one non-toxic pharmaceutical acceptable carrier.

11. A pharmaceutical composition comprising a compound of claim 1,2,3,4,5 or 6 and together with at least one non-toxic pharmaceutical acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/06831

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D223/12 C07D267/10 C07D243/08 A61K31/55 C07D207/22
C07D207/24 A61K31/40 C07D211/72 A61K31/445 C07D413/12
C07D471/10 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 11231 (G.D. SEARLE & CO.) 27 April 1995 see the whole document ---	1-11
E	WO,A,96 14844 (MERCK & CO., INC.) 23 May 1996 see the whole document ---	1-11
X	US,A,2 049 582 (K. ZIEGLER) 4 August 1936 see example 5 ---	1-5
X	US,A,3 121 093 (N.M. BORTNICK ET AL.) 11 February 1964 see the whole document ---	1-5
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 August 1996	21.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Allard, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010300., see BRN=390493 & AUST. J. CHEM., vol. 24, 1971, pages 371-5, ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010301 see BRN=6143647 & EUR. J. MED. CHEM. CHIM. THER., vol. 28, no. 1, 1993, pages 29-35, ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010302 see BRN=389517 and BRN=388043 & CHEM. PHARM. BULL., vol. 20, 1972, page 901 ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010303 see BRN=5981412 & SYNTH. COMMUN., vol. 13-14, 1989, pages 2237-42, ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010304 see BRN=778069 & BIOCHIM. BIOPHYS. ACTA, vol. 263, 1972, page 213, 215, 216 ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010305 see BRN=880305 & TETRAHEDRON LETT., vol. 19, 1965, pages 1411-19, --- -/--	1-5

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010306 .. see BRN=742055 & JP,A,68 017 189	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010307 see BRN=881955 & J. ANTIBIOT., vol. 26, 1973, page 625, 637	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010308 see BRN=777936 & J. ANTIBIOT., vol. 23, 1970, page 120, 121, 122, 123	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010309 see BRN=507189 & J. GEN. CHEM. USSR (ENGL. TRANSL.), vol. 32, 1962, page 464	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010310 see BRN=507962 & CHEM. BER., vol. 103, 1970, page 2505, 2506, 2508, 2511	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010311 see BRN=121698 & PROC. R. SOC. LONDON B, vol. 133, 1946, page 20, 53	1-5

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010312 see BRN=5403979 & ARCH. PHARM. BER. DTSCH. PHARM. GES., vol. 301, no. 10, 1968, pages 750-62, ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010313 see BRN=107123 & J. AMER. CHEM. SOC., vol. 77, 1955, page 761 ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010314 see BRN=141409 & J. ORG. CHEM., vol. 23, 1958, page 1954, 1956 ---	1-5
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002010315 see BRN=5508 & J. ORG. CHEM., vol. 23, 1958, page 1251, 1252, 1255, 1954, 1956 -----	1-5

INTERNATIONAL SEARCH REPORT

Int .tional application No.
PCT/US96/06831

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7-10 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compounds or compositions.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searched incompletely: 1-5, 7-11
Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte: nal Application No
PCT/US 96/06831

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9511231	27-04-95	AU-B- 8081194	08-05-95
		NO-A- 961403	09-04-96
WO-A-9614844	23-05-96	AU-B- 4462496	06-06-96
US-A-2049582	04-08-36	NONE	
US-A-3121093	11-02-64	NONE	